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Volume 44 • Number 1 • January–February 1977

MOUNT SINAI SCHOOL OF MEDICINE
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OF NEW YORK

THE MOUNT SINAI JOURNAL OF MEDICINE
• NEW YORK

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HOSPITAL
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Clinical Correlates of Diagnostic Microbiology
PART II

Festschrift in Honor of

S. STANLEY SCHNEIERSON, M.D.

SHALOM Z. HIRSCHMAN, M.D.,
Guest Editor

BLISHED BIMONTHLY AT MT. ROYAL AND GUILFORD AVES., BALTIMORE, MD. 21202 FOR THE MOUNT SINAI HOSPITAL, NEW RK, N. Y. 10029 BY THE COMMITTEE ON MEDICAL EDUCATION AND PUBLICATIONS, THE MOUNT SINAI HOSPITAL, FIFTH AVENUE ID 100TH STREET, NEW YORK, N. Y. 10029. SECOND-CLASS POSTAGE PAID AT NEW YORK, N. Y. AND AT ADDITIONAL MAILING FICES, COPYRIGHT 1977, THE MOUNT SINAI HOSPITAL.

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$\frac{4}{5} \div \frac{7}{8} = \frac{32}{35}$
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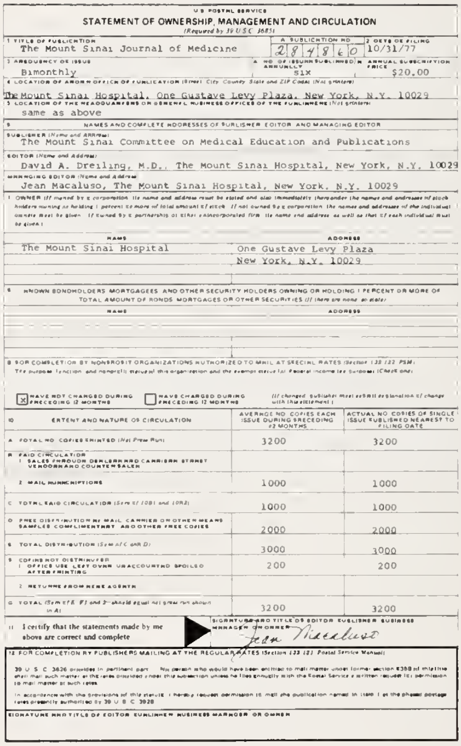

U S POSTAL SERVICE

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION

(Required by 39 U.S.C. 3685)

1 TITLE OF PUBLICATION: The Mount Sinai Journal of Medicine

A PUBLICATION NO: 2 8 4 8 6 0

2 DATE OF FILING: 10/31/77

3 FREQUENCY OF ISSUE: Bimonthly

A NO. OF ISSUES PUBLISHED ANNUALLY: six

B ANNUAL SUBSCRIPTION PRICE: $20.00

4 LOCATION OF KNOWN OFFICE OF PUBLICATION *(Street, City, County, State and ZIP Code) (Not printers)*: The Mount Sinai Hospital, One Gustave Levy Plaza, New York, N.Y. 10029

5 LOCATION OF THE HEADQUARTERS OR GENERAL BUSINESS OFFICES OF THE PUBLISHERS *(Not printers)*: same as above

6 NAMES AND COMPLETE ADDRESSES OF PUBLISHER, EDITOR, AND MANAGING EDITOR

PUBLISHER *(Name and Address)*: The Mount Sinai Committee on Medical Education and Publications

EDITOR *(Name and Address)*: David A. Dreiling, M.D., The Mount Sinai Hospital, New York, N.Y. 10029

MANAGING EDITOR *(Name and Address)*: Jean Macaluso, The Mount Sinai Hospital, New York, N.Y. 10029

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2 MAIL SUBSCRIPTIONS	1000	1000
C TOTAL PAID CIRCULATION *(Sum of 10B1 and 10B2)*	1000	1000
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F COPIES NOT DISTRIBUTED 1 OFFICE USE, LEFT OVER, UNACCOUNTED, SPOILED AFTER PRINTING	200	200
2 RETURNS FROM NEWS AGENTS		
G TOTAL *(Sum of E, F1 and 2—should equal net press run shown in A)*	3200	3200

11 I certify that the statements made by me above are correct and complete

SIGNATURE AND TITLE OF EDITOR, PUBLISHER, BUSINESS MANAGER, OR OWNER: Jean Macaluso

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Laboratory Diagnosis of Viral Infections: General Principles and Recent Developments*

G. D. HSIUNG, Ph.D.

INTRODUCTION

While various intensive studies have been made in animal virology in recent years, laboratory diagnosis of virus disease is still not widely practiced. Today viral diagnostic facilities are generally available in connection with research laboratories and are rarely operated within a clinical microbiologic setting. Undoubtedly, this is a reflection of the rigid procedures and operational expenses necessary for viral studies as well as of the limited number of well-trained personnel.

The significance of diagnostic virology was emphasized by us ten years ago (1, 2) and recently it has been reemphasized (3, 4). The main rationale for the laboratory diagnosis of viral infections is to obtain a precise diagnosis of the disease and to improve management of patient care. When antiviral chemotherapy becomes available, rapid diagnosis may be necessary to assist in the selection of the appropriate drug. Furthermore, the development of virus vaccines to control certain virus diseases is unquestionably dependent upon identification of the specific virus type responsible.

During the past ten years many new techniques have evolved, and new approaches are available for the recognition of viruses. It is now possible to make a diagnosis of viral infection not only by serologic tests but also by virus isolation methods (5, 6) and even direct electron microscopy (7). Since many different viruses are known to induce the same syndrome and, conversely, one virus may cause many diverse syndromes, it is often difficult if not impossible to make an etiologic diagnosis on the basis of clinical observation alone. Thus, one must rely on the laboratory for a definite answer.

In this paper I shall outline some of the essential techniques that are commonly applicable in a routine clinical laboratory for the isolation and identification of viruses together with some of the more recently developed procedures for their recognition and characterization. It is hoped that this review will be useful to laboratory workers as well as to physicians who are

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From the Department of Laboratory Medicine, Yale University School of Medicine, New

Requests for reprints should be sent to: G. D. Hsiung, Virology Laboratory, VA Hospital, West Haven, Ct. 06516.

* Parts of this paper are modified from G. D. Hsiung: *Diagnostic Virology*, Yale University Press, New Haven, 1973. Supported in part by the USPHS Research Grant AI08648 from the National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Md. and the Medical Research Service of the Veterans Administration.

interested in the diagnosis and management of patients having suspected viral illness.

IMPORTANCE OF SPECIMEN COLLECTION FOR VIRAL STUDIES

The successful isolation of viruses from clinical materials is largely dependent upon the proper collection and handling of specimens. Ideally, materials for viral studies should be collected and tested at bedside since many viruses are labile upon standing. All specimens should be taken as early as possible in the course of the disease and if the patient is hospitalized, on the date of admission. Specimens should be collected in sterile containers with protein-carrying medium, for example a 0.5% gelatin in Hanks' balanced salt solution (BSS) to stabilize the virus, and delivered to the laboratory promptly

The choice of specimens is largely dependent upon the clinical syndrome and/or the virus suspected. Because of the wide range of viruses responsible for similar clinical syndromes, it is common practice to include a set of specimens. Table I summarizes the preferred types of specimens to be collected from patients in accordance with the clinical syndromes which are commonly associated with different viruses. Blood samples are ordinarily used for serodiagnosis and should be obtained from all patients in addition to the specimens indicated. Paired sera, one collected at time of admission and one at convalescence, are very helpful, especially when virus isolations are unsuccessful. Blood, especially the leukocytes, may be used for virus isolation in selected cases.

In the laboratory all specimens received should be processed immediately for virus detection since many viruses are extremely sensitive to freezing-thawing. If storage is necessary, specimens should be held at 4°C and tested within 24 hours. If they must be kept for a longer time, they should be frozen at −70°C or lower but *not* at −20°C. In certain instances the successful recovery of infectious virus is dependent upon the viability of the tissue cells in which the viruses are present. Therefore, tissues obtained at biopsy or surgery should be treated accordingly, i.e., placed in a protein carrying medium for transport.

It should be noted that the laboratory cannot be expected to make a satisfactory test without mention of a clinical history and/or viruses suspected which assists greatly in the selection of an appropriate testing system, since each virus type has its preferred host spectrum (For details, see later sections).

METHODS COMMONLY USED IN A CLINICAL LABORATORY

Virus Isolation

Although the basic principles involved in the isolation and identification of viral agents are essentially the same as those for isolation and identification of bacteria, the viruses present greater difficulties because of their strict requirement for intracellular replication. The field is a rapidly developing one but there are certain standard methods that are now applicable for routine use.

TABLE I

Specimens to be Collected from Patients with Suspected Viral Infection

Virus Group Suspected	Clinial Disease Commonly Associated	Clinical Specimens[a] for Virus Isolation	Postmortem Materials
Enterovirus	poliomyelitis, aseptic meningitis, pleurodynia (Bornholm disease), myocarditis, pericarditis, herpangina	stool, rectal swab, throat swab, CSF, blood	spinal cord & other CNS tissues, blood, pericardial fluid, tissues with pathological lesions, colon contents
Rhinovirus	nonspecific febrile illness, common cold, afebrile URI	nasal washings, nasopharyngeal swabs	
Arbovirus	acute febrile illness, encephalitis, aseptic meningitis	blood	brain, CNS tissues, blood
Myxovirus	pharyngitis, croup, bronchiolitis, pneumonia, URI	nasopharyngeal washing, nasal swab, throat swab, blood, gargle washing, urine	lung, trachea, blood
	mumps	throat swab, blood, urine	
Measles virus	measles	throat swab, blood, urine	blood, CNS tissues, lung
Respiratory syncytial virus	croup, bronchiolitis, pneumonia	throat swab, nasal swab	lung, trachea, blood
Reovirus	respiratory illness (?), diarrhea (?)	throat swab, rectal swab, stool	stool, blood, lung
Rubella virus	rubella syndrome	throat swab, rectal swab, urine, CSF	placental & fetal tissues
Adenovirus	acute respiratory disease, pneumonia, pharyngeal conjunctival fever, keratoconjunctivitis, etc.	throat swab, rectal swab, stool, CSF, conjunctival secretions	lung, CNS tissues, blood, colon contents
Herpesvirus	herpetic gingivostomatitis, vulvo-vaginitis, keratoconjunctivitis, eczema herpeticum, encephalitis, cytomegalo-inclusion disease, varicella-zoster	vesicle fluid, throat swab or mouth washing, ulcer swab, CSF, blood, buffy coat, urine	CNS tissues, blood, other organs
Poxvirus	eczema vaccinatum, smallpox	local lesion fluid, pus, crust, blood	liver, spleen, blood

[a] For antibody determinations, acute-phase serum should be collected immediately after onset; convalescent serum should be collected 2 to 4 weeks after onset. Hsiung, G. D. *Diagnostic Virology*, Yale University Press, New Haven, 1973, p. 4.

Methods for virus isolation may vary from laboratory to laboratory. These variations depend upon the availability of cell culture systems, animal supplies, as well as personnel. Figure 1 shows a flow chart of procedures to be followed for the isolation and identification of viruses from clinical specimens. The selection of test system, whether cell monolayer, embryonated egg or infant mouse is based upon the type of virus suspected in relation to clinical

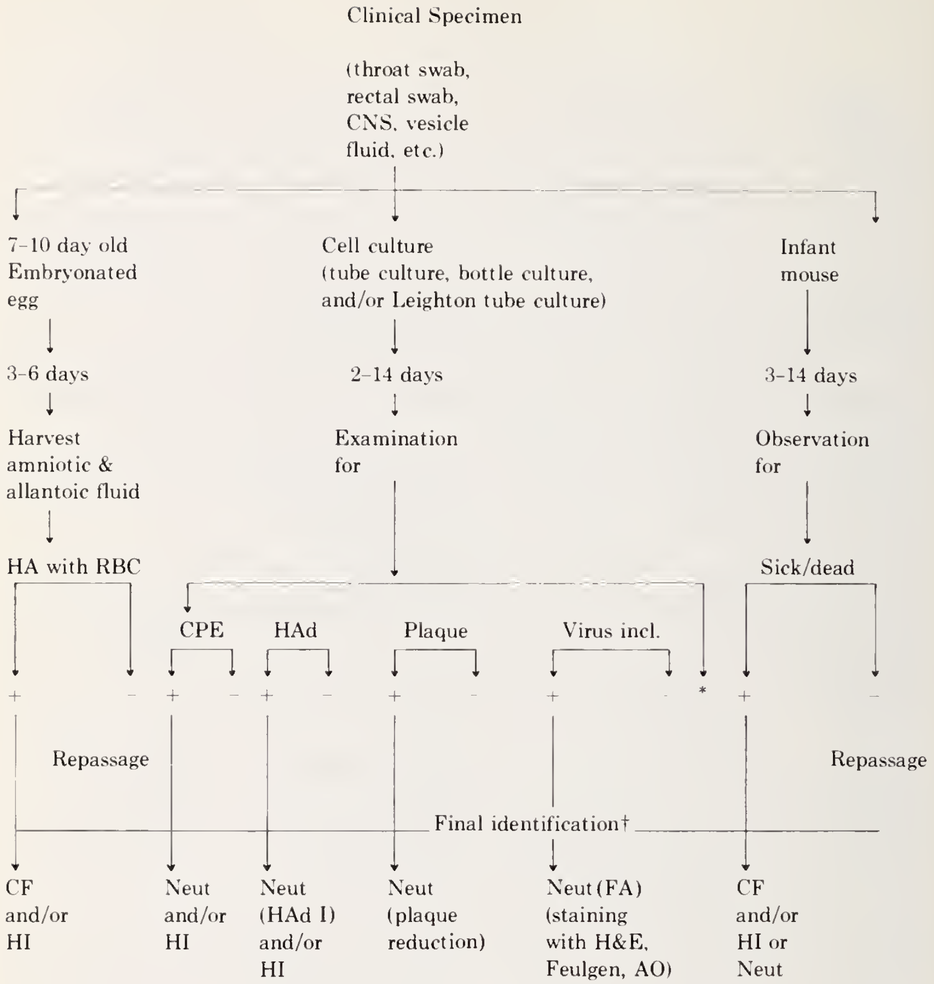
Clinical Specimen
(throat swab, rectal swab, CNS, vesicle fluid, etc.)
7–10 day old Embryonated egg
Cell culture (tube culture, bottle culture, and/or Leighton tube culture)
Infant mouse
3–6 days
2–14 days
3–14 days
Harvest amniotic & allantoic fluid
Examination for
Observation for
HA with RBC
Sick/dead
CPE
HAd
Plaque
Virus incl.
+
−
*
Repassage
Repassage
Final identification†
CF and/or HI
Neut and/or HI
Neut (HAd I) and/or HI
Neut (plaque reduction)
Neut (FA) (staining with H&E, Feulgen, AO)
CF and/or HI or Neut

FIG. 1. Flow chart for virus isolation and identification from Hsiung, G. D. *Diagnostic Virology*, Yale University Press, New Haven, 1973, p. 16. When a new agent is suspected, physical-chemical methods (p. 13, this article) can be used. + Serologic methods of choice for final identification vary according to the virus isolate.

diagnosis and patient history. However, the utilization of a variety of techniques increases the chances of recovering an agent (for details, see section on major virus groups).

Cell culture systems

Choice of cell culture. Various comprehensive studies on the susceptibility of different cell culture types to viral infection have shown that there is *no* single cell system which can serve as the choice cell type for virus isolation procedures. It is common practice to use several types of cell culture in order to recover the probable viral agents which might be encountered. Most enteroviruses grow well in primary monkey kidney cell cultures which are the preferred cell type for the isolation of the myxoviruses including influenza, parainfluenza and mumps viruses. The diploid cell strains of human embryonic fibroblast cell cultures, for example WI-38, are by far the superior cell type for isolating rhinoviruses and cytomegaloviruses. On the other hand, continuous human heteroploid cell lines such as Hep-2 cells are best for detecting adenoviruses, respiratory syncytial virus (RS) and coxsackievirus group B. However, Hep-2 cells are insensitive for the isolation of echoviruses and coxsackievirus group A.

In a routine laboratory, a set of cell cultures including a primary monkey kidney cell culture, a human diploid cell strain, and a human heteroploid cell line is sufficient for detecting most of the viral agents commonly encountered in human disase. Primary human embryonic kidney cell cultures would be preferable to most other human cell types but since they are expensive and often in short supply, they are seldom used for routine purposes. A wide variety of primary and serially passaged cell cultures, including those mentioned, are now available commercially or can be prepared by individual laboratories with appropriate facilities.

Cellular changes in fluid culture. Once the cell cultures are inoculated with clinical specimens, they are incubated at 33°–35°C and kept for examination for at least two weeks or longer for evidence of virus-induced cellular changes, primarily cytopathic effect (CPE). In certain cases cytopathology is characteristic for a particular virus group and the pattern can be used to differentiate between members of the various major virus groups (Fig. 2). For example, CPE induced by an enterovirus in primary monkey kidney cell cultures (Fig. 2C) and Hep-2 cells (Fig. 2D) is distinguishably different from that induced by the adenoviruses (Figs. 2E and F) or herpes simplex virus (Figs. 2G and H). Some agents which fail to produce recognizable cellular changes, may be detected by indirect techniques, for example, recognition of myxovirus-infected primary monkey kidney cell cultures by hemadsorption (Fig. 2I) or detection of rubella virus by interference phenomena. Many viruses induce syncytial cell formation in Hep-2 cells, as in the case of respiratory syncytial virus and parainfluenza viruses (Fig. 2J). Occasionally blind passage may be necessary to reach high enough concentrations of virus to produce evidence of its presence.

Plaque formation under agar overlay. The formation of virus plaques under agar-containing overlay medium is somewhat analogous to bacterial colonies on solid media. This is done either in bottle cultures or in petri dishes. After the fluid is removed from the monolayer cultures and the specimen inoculated, the cell sheet is covered with agar overlay medium containing neutral red, a vital dye. As virus replication occurs, cell degeneration or death is demonstrated by the presence of decolorized areas or plaques while the surrounding live cells remain stained by the dye (Fig. 3). Plaque size and shape are often characteristic for different viruses and plaque morphology is a useful tool for the recognition and characterization of the enteroviruses, Figure 3A (8). Furthermore, the plaque method appears to be more sensitive than CPE method for the isolation of enteroviruses from clinical specimens in which the number of virus particles is too small to be detected by other means (9).

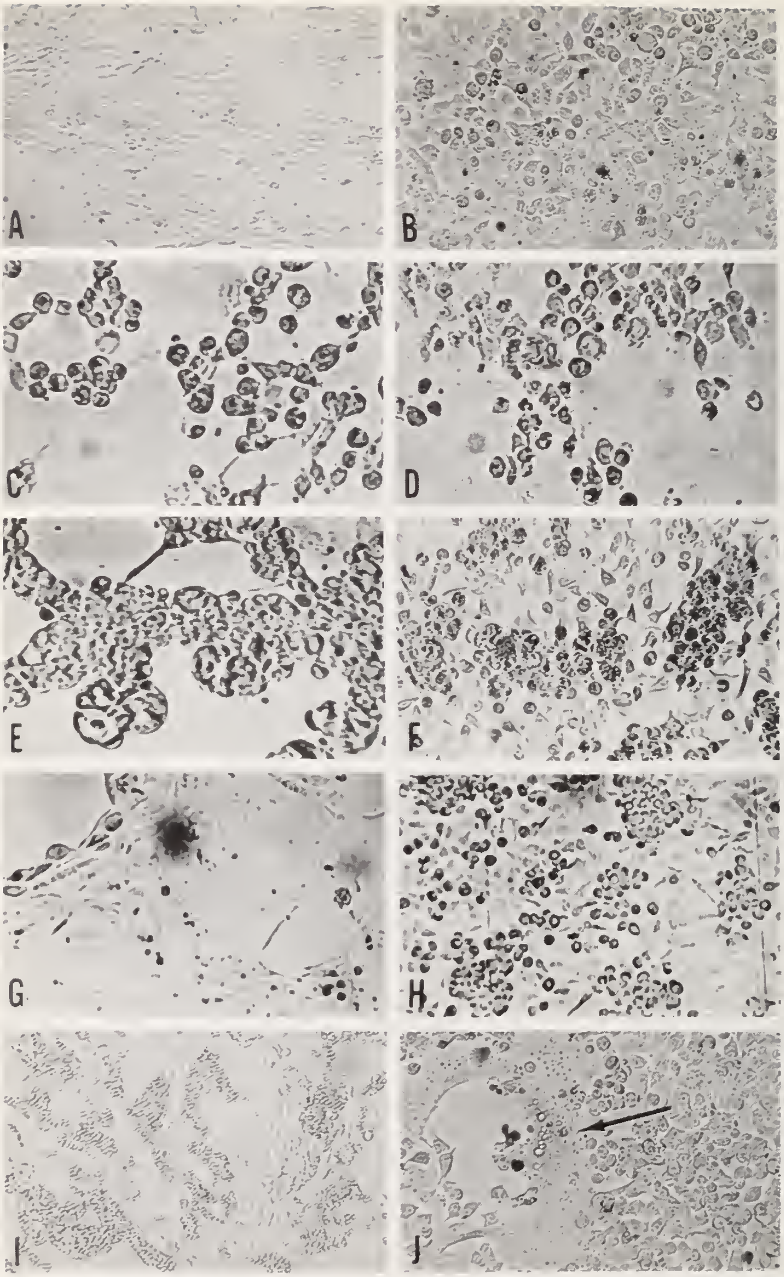

FIG. 2. Virus-induced cellular changes in primary monkey kidney cell cultures (panel at left) and Hep-2 cell cultures (panel at right), 100×. A. & B. Non-infected control cultures; C. & D. CPE induced by poliovirus type 1; E. & F. CPE induced by adenovirus type 3; G. & H. CPE induced by herpes simplex virus type 1; I. & J. Hemadsorption and syncytial cell formation induced by parainfluenza virus types 1 and 3 respectively.

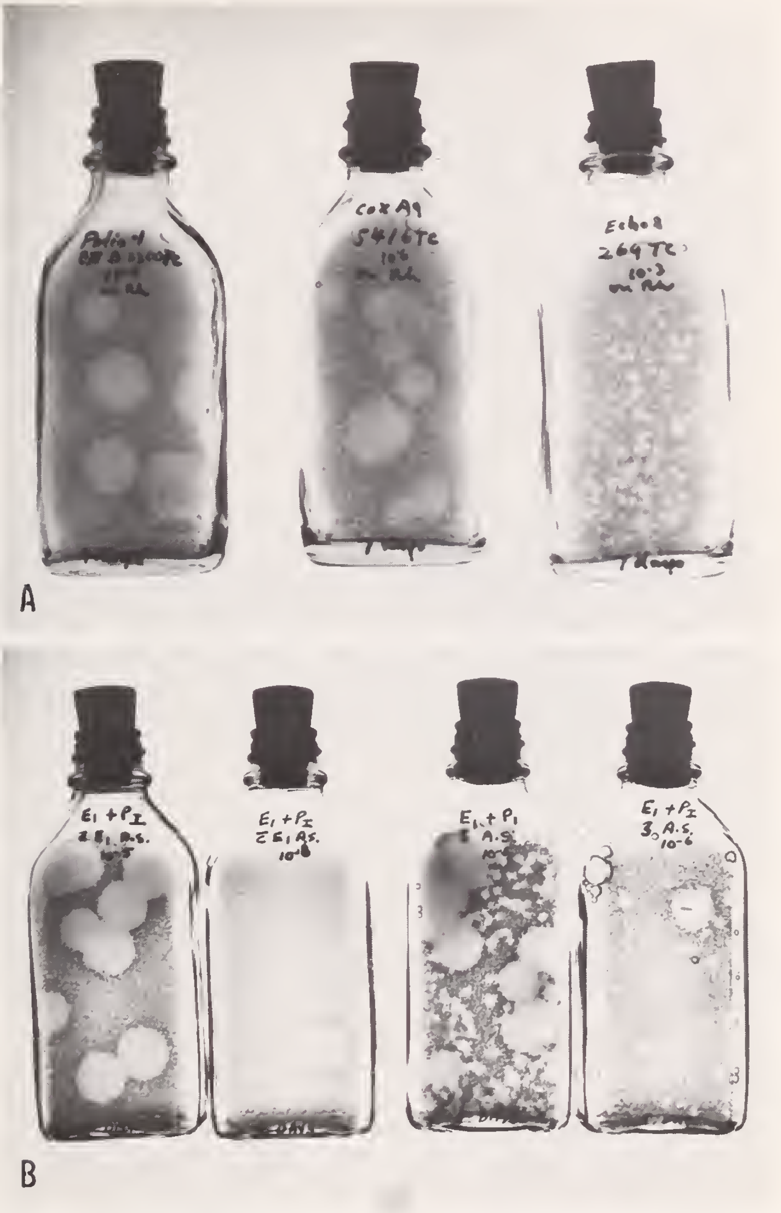
Polio 1
cox A9
5416TC
10-6
Echo 8
264 TC
10-3
A
E1 + PI
E1 + PI
E1 + P1
A.S.
E1 + PI
A.S.
10-6
B

FIG. 3. Enterovirus plaques under agar overlay medium. A. Plaque morphology of poliovirus type 1 (left) and coxsackie A9 (center) and echovirus 8 (right). B. Mixed infection of enteroviruses (two bottles at right) and in presence of echovirus 1 antiserum (two bottles at left showing only poliovirus plaques).

Certain virus strains do not produce CPE but nevertheless do form plaques, as in the case of certain arboviruses. In cases of mixed infections the plaque method is far more efficient for the recognition of two types of viruses (Fig. 3B).

Problems of endogenous virus contaminants. From time to time primary cell cultures have been found to harbor one or two types of endogenous viruses. These are particularly frequent in primary kidney cells derived from monkey tissues (10, 11) as well as from some non-primate tissues (12, 13). Many of these endogenous agents induce CPE or hemadosorption or they may even interfere with replication of the virus in the specimens being tested. Since the presence of mycoplasma has been reported in a number of cell lines (14, 15), it is good practice to examine the various cell strains or cell lines for the presence of these organisms. The diagnostic virologist should always be aware of the possibility of endogenous contaminants and must be able to recognize their presence and not confuse them with virus isolates from clinical specimens.

Newborn mice

Although animal inoculation has been largely replaced by tissue culture systems for isolating viruses, newborn mice are still the host system of choice for isolating certain types of coxsackie A virus and most arboviruses. It is costly and certainly impractical to inoculate all specimens into newborn mice. Only in selected instances, for example for patients with herpangina or with suspected arbovirus encephalitis, should specimens be inoculated into newborn mice, either intracerebrally or intraperitoneally.

Embryonated chicken eggs

Embryonated eggs are still preferable for the isolation of certain strains of influenza A virus (16) although influenza B viruses are readily detected in primary monkey kidney cell cultures. If smallpox virus is suspected, the inoculation of the chlorioallantoic membrane is a useful technique for differentiating this virus from vaccinia virus and herpes simplex virus by pock size as well as from varicella-zoster virus which does not produce pocks on this membrane.

Serologic Tests

Complement-fixation, hemagglutination-inhibition and neutralization test

At present the most frequently used serologic tests are complement-fixation (CF), hemagglutination-inhibition (HI), and neutralization tests. The latter includes inhibition of virus-induced CPE, plaque reduction or inhibition of hemadsorption phenomena. Selection of which of these tests to perform is determined by the virus type involved and the information being sought. Performance of one or another either alone or in combination will a) identify an isolate by testing it against specific antisera, b) confirm the patient's infection by demonstrating a rise in antibody against the virus isolated or the prototype virus strain, and c) establish a diagnosis by screening acute and convalescent serum samples for antibody rises against several viruses considered to be likely etiologic agents, especially when no agent has been isolated from the clinical specimens. The development of microtiter technique in recent years has been a great advance in performing serologic tests (17). This method has been applied to tests involving many virus types including neutralization test for picornaviruses (18). In general, because so many viruses are now known, serodiagnosis is performed only in selected situations. It is usually a retrospective diagnosis after the patient has recovered and is of limited value in clinical medicine. However, where isolation of virus is slow or where the serologic results can be more rapidly obtained than a virus isolation, as in the case of the HI test for rubella virus (19), serodiagnosis can be extremely useful.

Immunofluorescence

These techniques have long been applied for the diagnosis of human influenza virus in nasal smears (20, 21) but the methods are still not widely used for diagnosis of virus infection of the respiratory tract. Part of the problem may be due to the small quantity of virus particles or antigen available as well as the difficulties inherent in selecting a suitable reagent for the hundreds of possible virus types that may be present in a clinical specimen. The techniques described by Sommerville for rapid diagnosis of virus infection of the central nervous system by examination of cell pellets from cerebral spinal fluid (22) or for determining the presence of viral antigen in leukocytes and macrophages (23) appear to be promising but in each instance preliminary cultivation procedures are necessary as has been described for the detection of Epstein-Barr virus in cultured leukocytes using fluorescent antibody techniques (24). Certainly the method offers a great advantage in the detection of rabies virus infection in brain tissue when only one virus type is involved (25).

Immunodiffusion

These tests have been used for detecting hepatitis B (serum hepatitis) antigen which is found in significant quantities in certain blood samples. The method commonly used is the Ouchterlony agar-diffusion procedure which is slow and insensitive and has been modified by investigators working in these areas (26, 27). To improve the antigen-antibody precipitation reaction, more rapid and sensitive procedures have been developed such as the electrophoretic and radioimmunoassay methods.

RECENT DEVELOPMENTS

Cultivation of Cells or Tissues for Isolation of "Slow" Viruses

It has become apparent in recent years that in order to recover "slow" viruses from infected tissues, especially those in a latent state, the inoculum must contain viable cells, i.e., cultivation of cells in order to recover infectious virus. Although the original isolation of human adenovirus was obtained from a spontaneous degenerated cell culture derived from human adenoid tissue (28), cell culture propagation for isolating human virus has not been a common practice. On the other hand, animal viruses, particularly those of simian origin, to a large degree have been isolated as the result of spontaneous degeneration of cell cultures. The recovery of large numbers of simian viruses (10, 11) has been due to the extensive use of monkey kidney cell cultures in virus research and for the preparation of virus vaccines.

Cultivation and cocultivation

The terms cultivation and cocultivation refer to those techniques whereby fresh tissues are dispersed with trypsin and the resultant cells are grown out into monolayer cultures for long-term cultivation and observation for virus induced cellular changes, or the trypsin-dispersed cells are cocultivated with virus-susceptible cell monolayer cultures and the latter are observed for the development of cytopathic effect. Although it has been known for many years that varicella-zoster virus could be passaged best using infected viable cells (29), the superiority of viable cells over tissue homogenates (a method commonly used for virus isolation) for recovery of infectious virus from infected tissues has only recently been recognized, especially when dealing with slow virus infections of the central nervous system. Although the presence of measles virus antigen was detected in cultured brain cells from patients with subacute sclerosing panencephalitis (SSPE) by the immunofluorescent staining technique, the isolation of infectious measles virus was not made until the brain cells were cocultivated with HeLa cells (30) or with green monkey kidney cells, BSC-1 cell line (31). Furthermore, a papovavirus related to SV40 was isolated from the brain cells of patients with progressive multifocal leukoencephalopathy (PLM) when cocultivated and fused with primary green monkey kidney cells (32) although in this instance another papovavirus, the JC virus, was also isolated from the brain homogenate obtained from a PML patient (33). These cultivation and cocultivation techniques will probably receive wide use in the near future for the recovery of viruses from other chronic diseases of suspected viral etiology.

Organ culture

The use of organ culture techniques in virology is a relatively recent development which has facilitated the isolation and recognition of many respiratory viruses. Essentially the method entails the cultivation of small tissue explants in special medium and under conditions in which growth of undifferentiated cells is restricted while the normal architecture and function of the tissue is maintained. The presence of virus can be determined by fixation of the cultured tissues followed by staining and observation for virus induced pathology. Many rhinovirus strains were originally isolated by the use of nasal or tracheal epithelial organ culture derived from human embryo (34). The isolation of coronaviruses also requires the use of ciliated tracheal organ culture (35). Undoubtedly by cultivating explants of other tissues, additional viruses probably will be isolated from human diseases with unknown etiology.

The Use of Electron Microscopy for the Recognition and Detection of Viruses

The size and shape of a virus can be determined by direct electron microscopic (EM) examination. The techniques most commonly used include negative staining of virus particles with electron-dense salts of phosphotungstic acid or preparation of ultrathin sections of cells or tissues suspected of harboring virus. Electron microscopy has been applied for the diagnosis of pox virus and herpesvirus infection for almost thirty years (36), but this technique has not been widely used until recently. Recognition of more than one kind of virus-like particles in sera of patients with Australia antigen associated with hepatitis was made possible only by electron microscopy (37). The development of immune electron microscopy for the recognition of virus particles in clinical specimens as well as for serodiagnosis has opened a whole new era in diagnostic virology.

Rapid diagnosis of poxvirus and herpesvirus infections

Visualization of poxvirus particles in crust extracts or in vesicle fluid can be made within a few hours when electron microscopic examination is undertaken. Where smallpox is suspected the electron microscope can be helpful for an early presumptive diagnosis (38). Other investigators have reported the advantages of using electron microscopy for the differentiation of herpesvirus and poxviruses in skin lesions (39, 40). In fact, the recognition of a herpesvirus, the Epstein-Barr virus, in cultured lymphoblastic cells derived from a Burkitt lymphoma patient was originally made using electron microscopy (41).

Recognition of human papovavirus

The first human papovavirus particle was observed by electron microscopy in a human skin papilloma as early as 1953 (42), but methods for cultivation of this virus are still not available. The recognition of another human papovavirus in the brain cells of patients with a rare demyelinating disease, progressive multifocal leukencephalopathy (PML), was also made by electron microscopy (Fig. 4A) (43) several years before the virus was isolated (32, 33). In the field of neurovirology the isolation and cultivation of human papovavirus in cell culture was one of the most exciting recent developments.

Recent developments in immune electron microscopy

The technique of immune electron microscopy has advanced rapidly and provides a useful, more sensitive refinement than simple electron microscopic examination. This is done by mixing stool filtrate and convalescent serum prior to centrifugation for electron microscopy. Using immune electron microscopy techniques virus particles 22–27 nm in diameter in stool samples were observed (Fig. 4B) (44). These particles were later identified as members of the parvovirus group. On the basis of serologic evidence obtained through the use of immune electron microscopy, it was concluded that these virus particles are associated with non-bacterial gastroenteritis. Using the same technique, another parvovirus-like agent was observed in the stools from patients with hepatitis A (45).

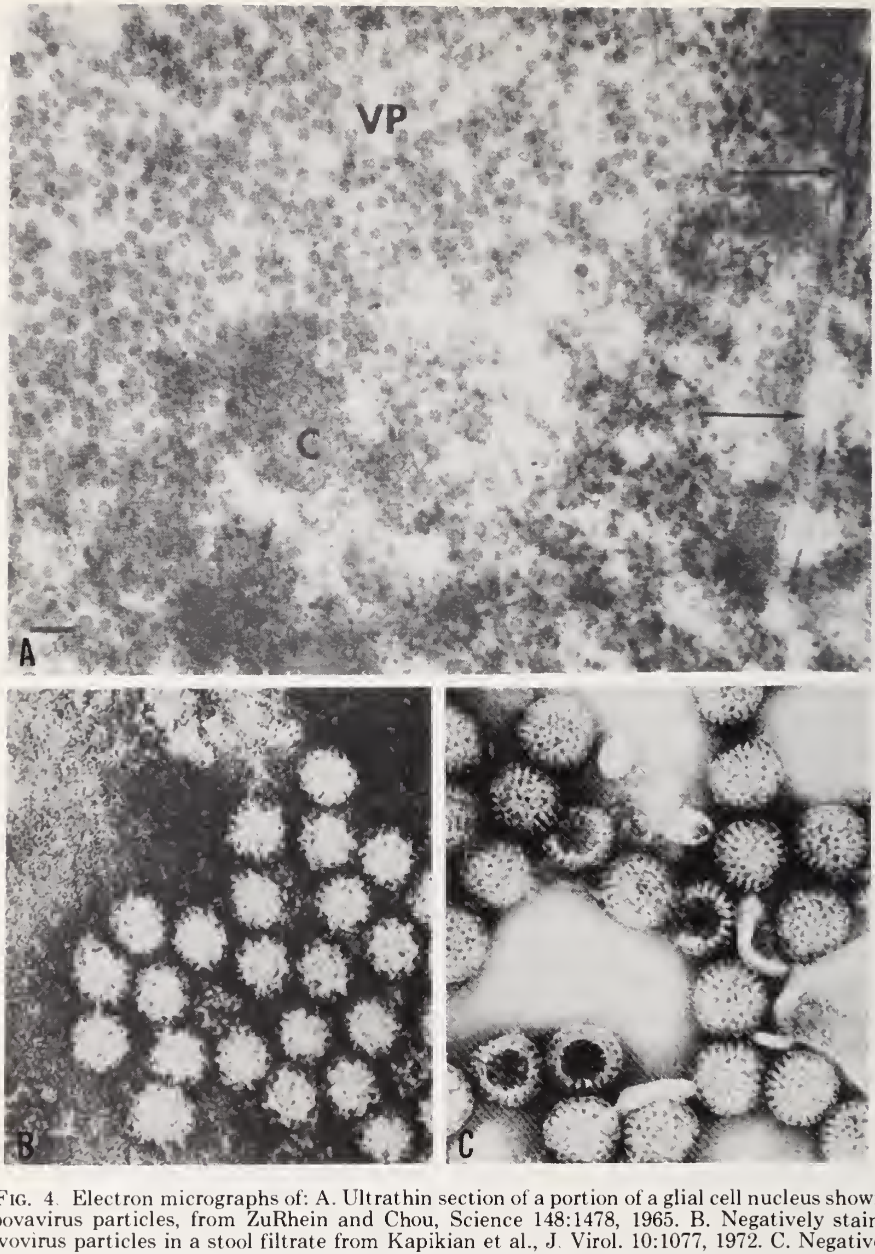

Fig. 4. Electron micrographs of: A. Ultrathin section of a portion of a glial cell nucleus showing papovavirus particles, from ZuRhein and Chou, Science 148:1478, 1965. B. Negatively stained parvovirus particles in a stool filtrate from Kapikian et al., J. Virol. 10:1077, 1972. C. Negatively stained reovirus-like particles in a stool filtrate from Kapikian et al., Science 185:1050, 1974.

Another important finding was the recent observation of reovirus-like particles by the electron microscopic examination of fecal extracts obtained from patients with infantile diarrhea (46, 47, 48). Virus particles, 67 to 73 nm in diameter, were observed in large quantities in some stool samples (Fig. 4C). Many virus particles with a definite double-shelled capsid, as well as empty particles were observed.

The field of diagnostic virology has certainly been widened through the use of immune electron microscopy, particularly when dealing with fastidious agents for which cultivation procedures have not been developed. In those instances where a particular virus infection is suspected but cannot be isolated, serodiagnosis using immune electron microscopy can be carried out. Thus electron microscopy provides a valuable adjunct to more conventional procedures in the diagnosis of viral diseases.

Physical-Chemical Methods for Characterization of "New" Viral Agents

As described above, procedures used for the isolation and identification of viruses are now fairly well standardized. With highly trained personnel, a virus laboratory can perform most of the routine diagnostic tests and identify agents commonly encountered in a clinical laboratory. However, the identification of a "new" virus or a new variant strain of a known agent may present problems. It may be necessary to characterize the physical and chemical properties of the new agents in order to facilitate identification. These include nucleic acid type (RNA or DNA), size and shape, and ether sensitivity in order to characterize the agent's basic properties.

Nucleic acid determination

The nucleic acid type can be determined by a number of methods. However, since these methods are indirect, interpretation of results should be considered tentative until more refined methods of nucleic acid extraction are employed. In general, the multiplication of DNA viruses is inhibited by 5-fluoro-2-deoxyuridine (FUDR) or 5-bromo-2-deoxyuridine (BUDR), whereas multiplication of RNA viruses is not affected by these compounds. For example, in a Hep-2 culture containing BUDR at a concentration of 40 μg per ml, CPE induced by herpes simplex virus (a DNA virus) is completely inhibited, whereas CPE induced by an enterovirus (a RNA virus) is not affected (49).

In selected instances, nucleic acid type can be determined by the use of acridine orange staining technique and/or Feulgen reaction (50). The appearance of a yellowish-green inclusion in the nucleus after acridine orange staining or a brilliant red inclusion in a cell stained by the Feulgen reaction is an indication that the nucleic acid of the virus is probably DNA.

Electron microscopy, in addition to revealing viral structure, can also be used to determine nucleic acid type since DNA viruses generally stain intensely with uranyl acetate, whereas the RNA viruses do not (51). These techniques, either individually or in combination, have been used for the determination of the nucleic acid of a variety of viruses.

Ether sensitivity test

Determination of ether sensitivity is readily accomplished by exposing the virus suspension to ether for 1–2 hours followed by testing for virus infectivity Loss of infectivity indicates sensitivity due to the destruction of the lipid containing envelope surrounding the virus particle whereas retention of infectivity indicates a lack of such a lipid containing structure and consequently a resistance to ether treatment.

Ultrafiltration for virus size determination

Although the size and shape of a virus can be determined directly by electron microscopy, other, more accessible means for estimating virus particle size have been developed. One of the simplest and oldest methods for determining virus particle size is ultrafiltration. This is usually done by passing a virus suspension through a series of collodion membranes of graded porosity. The size of the virus is measured grossly by its ability to pass through or be retained by the filter. Despite some limitations and complications that have been encountered, the availability of membrane filters and suitable equipment has brought the ultrafiltration procedures within the scope of a routine laboratory (52). The equipment used for filtering small amounts of virus-containing fluid includes a 2-ml syringe attached to Swinny adapters connected to a hypodermic needle. After clarification through a membrane with a 450- or 300-mμ pore diameter, the virus fluid is further filtered through a test membrane of 100 or 50 mμ. A 20-ml Vacutainer (Becton, Dickinson & Company, Rutherford, N. J.) tube is used to collect the filtrate. Virus infectivity of the suspension is determined before and after filtration, and virus size is estimated according to the virus infectivity retained in the filtrate. Large size viruses lose their infectivity when 100 mμ and 50 mμ pore diameter membranes are used. Medium size viruses pass through 100-mμ but not through 50-mμ membranes and small viruses pass through both the 100- and 50-mμ membranes. Figure 5 illustrates how size can be used for preliminary grouping of both DNA and RNA viruses. Thus, by utilizing a few simple tests to determine certain physical-chemical properties as well as estimating size it is possible to place a newly isolated agent within one of the major virus groups.

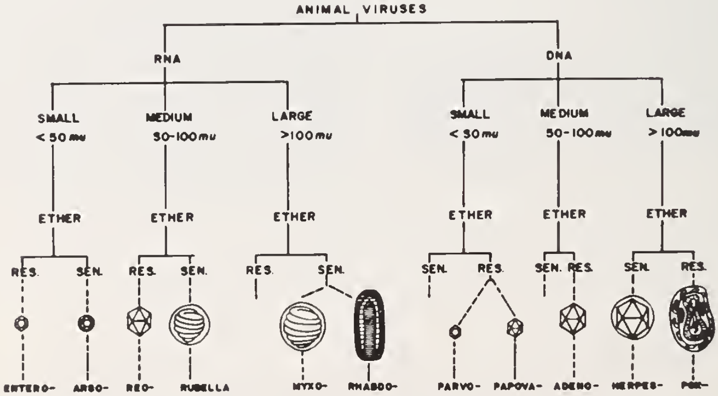
ANIMAL VIRUSES
RNA
DNA
SMALL
< 50 mu
MEDIUM
50-100 mu
LARGE
>100 mu
SMALL
< 50 mu
MEDIUM
50-100 mu
LARGE
> 100 mu
ETHER
ETHER
ETHER
ETHER
ETHER
ETHER
RES.
SEN.
RES.
SEN.
RES.
SEN.
SEN.
RES.
SEN.
RES.
SEN.
RES.
ENTERO-
ARBO-
REO-
RUBELLA
MYXO-
RHABDO-
PARVO-
PAPOVA-
ADENO-
HERPES-
POX-

FIG. 5. Major grouping of viruses. Hsiung, G. D.: *Diagnostic Virology*, Yale University Press, New Haven, 1973. p. 52.

TABLE II

Picornaviruses of Man

Virus subgroup	Total No. virus types	Acid sensitivity (pH 3)	Cell culture spectrum				Mouse Pathogenicity
			RhMK	WI-38	Hep-2	RK	
Enteroviruses		Stable					
Poliovirus	3		+[1]	+	+	–	–
Coxsackievirus B	6		+	+	+	–	+
Coxsackievirus A	24		±	±	–	–	+
Echovirus	34[2]		+	±	–	–	–
Rhinoviruses	89	Labile	±	+	–	–	–

[1] + virus-induced CPE or death of mouse, ± certain strains showed CPE, – No CPE observed nor mouse death.

[2] Echovirus 9 is identical to Coxsackie A23. Echovirus 10 has been reclassified reovirus 1. Echovirus 28 has been reclassified rhinovirus 1A. Echovirus 34 is a prime strain of Coxsackie A24.

MAJOR VIRUS GROUPS COMMONLY ENCOUNTERED IN A CLINICAL LABORATORY

The agents associated with many common viral infections may differ from season to season, or year to year, and also in relation to geographic location. In the following section, examples are given for the detection of some of the more common viral agents which are responsible for most viral illnesses in temperate climates for which laboratory diagnosis is sought.

The Picornaviruses (Enteroviruses and Rhinoviruses)

The picornaviruses are small stable RNA viruses, 20–30 nm in diameter, and resistance to ether treatment. There are two subgroups, the enteroviruses and the rhinoviruses, which can be separated by their sensitivity to acid treatment (Table II). Rhinoviruses are inactivated after treatment with a medium at pH 3 for one to two hours whereas enteroviruses are not affected by such treatment.

Enteroviruses

The human enteroviruses include poliovirus, coxsackievirus groups A and B, and the echoviruses (53). They are transient inhabitants of the alimentary tract. Infection with enteroviruses are common the year round in tropical and subtropical areas, but in temperate climates there is a sharp seasonal incidence with peaks in the summer and fall. Virus dissemination is primarily from person to person and the infections are highly contagious. Clinical diseases associated with enteroviruses are indicated in Table I. These include a wide spectrum of illnesses from mild nonspecific febrile to severe poliomyelitis and aseptic meningitis.

Virus isolation in tissue culture. The enteroviruses are recovered readily from throat swabs, rectal swabs of fecal specimens from infected individuals. Excretion of virus in the feces often persists for several weeks, but recovery of virus from the blood is rare although viremia is common during the incubation period.

Isolation in tissue culture is the method of choice for making a diagnosis of enterovirus infection. Most laboratories can isolate the enteroviruses by using a combination of two or three cell culture systems including primary monkey kidney cells and one human cell line, for example, Hep-2 cells. Growth of some of the group A coxsackieviruses requires inoculation into newborn mice.

Identification of isolates. All enteroviruses induce a recognizable CPE (Figs. 2C and D) which can be easily differentiated from that produced by other major virus groups (Fig. 2 E–H) that may be present in throat swabs of fecal specimens. Poliovirus and coxsackievirus B grow well in the Hep-2 cell line but coxsackievirus A and echoviruses generally do not produce CPE in these cells (Table II). In addition, plaque size and shape induced by the polio, coxsackie and echoviruses are distinctly different (Figure 3A). Thus, advantage is taken of the differential host cell range and plaque morphology to separate poliovirus and coxsackievirus group B from coxsackievirus group A and echoviruses in a manner analogous to the use of selective media in diagnostic bacteriology (8). Through these means a presumptive diagnosis sometimes can be made as soon as CPE appears in selected cell culture systems, sometimes within 1 or 2 days. The ability to report presumptive diagnosis of a viral infection without waiting for the specific serotyping of the isolate is of real value in the clinical management of a patient. Final identification of a serotype depends upon type specific serum neutralizing tests and this is most readily accomplished by use of interesecting pools of hyperimmune antiserum (54, 55).

Mixed infection. If a virus isolate cannot be identified by the routine neutralization test using known typing sera, a new enterovirus or a mixture of viruses may be present. With the widespread use of oral poliovirus vaccines it is not unusual to isolate the vaccine strain along with other enteroviruses from recently vaccinated persons. If the agents grow in tissue culture, mixtures often can be detected promptly by utilizing plaque morphology and differential cell cultures. An example, as shown in Figure 3B, is the recognition of a poliovirus and an echovirus in a fecal specimen by the appearance of two different types of plaques in a rhesus monkey kidney cell culture (two bottles at right). In the presence of antiserum to the small plaque virus, only the large plaque virus, subsequently identified as poliovirus type 1, was seen (two bottles at left).

Rhinoviruses

Rhinoviruses are primarily isolated from patients with respiratory illness. Throat washings or nasal swabs are choice specimens for virus isolation. Human diploid continuous cell strains, for example WI-38 human embryonic lung cells, appear to be the most sensitive system for isolating rhinoviruses. Typical CPE induced by rhinoviruses is similar to that induced by enteroviruses but they can be separated most readily by their sensitivity to acid treatment (pH 3.0). At present, there are 89 serotypes as well as many isolates that are awaiting definitive typing (56).

The Myxoviruses

The myxoviruses are large RNA viruses, 100–150 nm in diameter, with a lipid-containing envelope (57). They are sensitive to ether treatment and are relatively heat labile. The influenza viruses and parainfluenza viruses are the true myxoviruses, and are also known as orthomyxovirus and paramyxovirus respectively (58), whereas measles and R. S. viruses, which morphologically resemble the myxoviruses but are biologically distinct from them, are known as pseudomyxoviruses (6) (Table III). Influenza viruses are usually associated with epidemic respiratory disease in all age groups while the parainfluenza viruses are generally associated with respiratory infections in children.

Influenza and parainfluenza virus isolation

These viruses are prevalent in the winter months and are commonly associated with respiratory diseases (Table I). Throat washings or swabs or nasopharyngeal swabs are the clinical specimens generally used for virus isolation. Inoculation by amniotic route of 10–11 day old embryonated eggs is the method of choice for primary isolation of influenza viruses, although primary monkey kidney cell cultures can also be used, particularly when embryonated eggs are not available.

Generally neither influenza nor parainfluenza viruses produce CPE in monkey kidney cultures. Recognition of their presence can be determined by the hemadsorption phenomenon whereby the infected cells adsorb guinea pig erythrocytes which, when added to the infected culture, adhere and form clumps (Fig. 2I). In certain instances parainfluenza viruses also induce syncytial cell formation in Hep-2 cultures (Fig. 2J). Serologic identification of an isolate can be made by the hemagglutination-inhibition test in the case of the influenza viruses or by hemadsorption inhibition in the case of the parainfluenza viruses using type-specific antisera.

TABLE III

Myxoviruses of Man

Virus subgroup	types	Cell culture system				Mouse Pathogenicity	Embryonated egg fluid
		RhMK	WI-38	Hep-2	RK		
Orthomyxo virus	Influenza virus types A, B, C	+[1]	±	±	–	–	+[2]
Paramyxovirus	Parainfluenza types 1–5	+[1]	±	±	–	–	±
	Mumps	+	+	±	–	–	+
Pseudomyxovirus	Respiratory syncytial virus (R.S.)	±[3]	±	+[3]	–	–	–
	Measles	+[3]	–	+[3]	–	–	–

[1] Hemadsorption positive +; certain strains only, or poor growth ±; no hemadsorption, –.

[2] Hemagglutinin positive +; no hemagglutinin, –.

[3] Syncytial cell formation.

Mumps virus

The routine diagnosis of mumps virus infection generally is made by serologic tests although virus isolation can also be done. Freshly collected urine samples as well as oral swabs or washings are used for mumps virus isolation. Primary monkey kidney cells and embryonated eggs are the test systems of choice. The ability of mumps virus infected cultures to adsorb guinea pig erythrocytes resembles other members of the true myxovirus group. A significant rise in complement-fixation or hemagglutination-inhibition antibody titer during the course of the illness confirms the probability of mumps virus infection, although cross reactions between mumps and certain parainfluenza viruses have been observed.

Respiratory syncytial virus

This virus can be recovered from throat and nasal swabs. Since the virus is extremely labile, inoculation of the specimen into tissue culture, for example Hep-2 cells, should be done without prior storage. The CPE induced, which has a characteristic syncytial pattern, is often slow in developing and it is necessary to observe the cultures for at least two weeks.

Measles and rubella

Rubella virus is as yet unclassified, but for the convenience of discussion, it is mentioned here. Since the clinical diseases induced by measles and rubella virus are easily recognized and virus isolation methods are slow, the latter are not commonly performed. Serologic tests are often used to determine the immune status of a person who has been exposed to an overt case of measles or rubella. The hemagglutination-inhibition test serves as the most rapid and simplest serologic test for determining antibody which appears rapidly after onset of rash and persists for many years.

The Adenoviruses

The adenoviruses are medium size DNA viruses, 60–80 nm in diameter. Members of this group are relatively stable ether-resistant viruses which possess a common group-specific complement-fixing antigen (59). There are 33 human adenovirus serotypes. The clinical symptoms of adenovirus infection vary from pharyngitis and conjunctivitis to undifferentiated upper respiratory infection.

Virus isolation in tissue culture

The adenoviruses are readily isolated from throat swabs or fecal specimens when human cell cultures are used. Clusters of large rounded cells, typical of adnovirus infection (Figs. 2E and F), are easily recognized. Most adenovirus types exhibit hemagglutination with monkey or rat erythrocytes but types 18 and 31 lack this property. Identification of adenoviruses is based upon reaction to a common group-specific antigen by complement-fixation test using human reference serum containing known adenovirus antibody. However, neutralization test in cell culture is necessary for identification of specific virus types.

Mixed infections with an adenovirus and a myxovirus have been observed from time to time in clinical specimens and difficulties have been encountered in separating and identifying these mixed infections. An example is illustrated in Figure 6. In this instance the parainfluenza virus induced multinucleated syncytial cells in the Hep-2 whereas the adenovirus induced typical intranuclear inclusions. Following subculture of such a mixture into monkey cells, only the parainfluenza virus was obtained, as determined by hemadsorp-

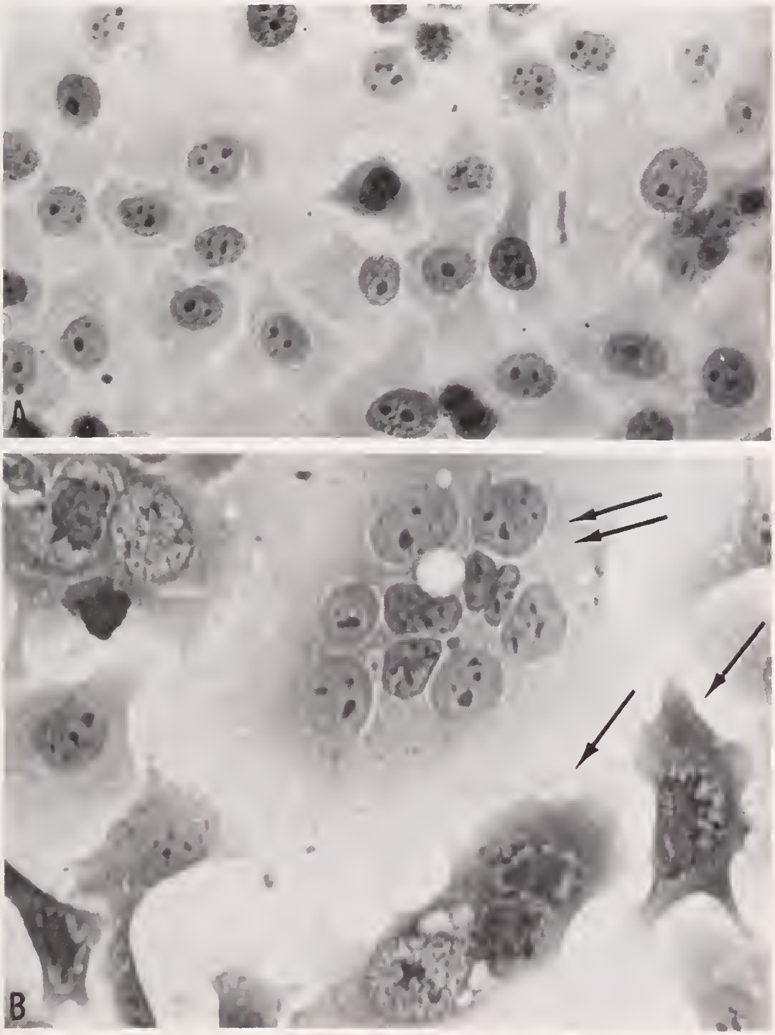

FIG. 6. Mixed infection of an adenovirus and a myxovirus in Hep-2 cell cultures. Hematoxylin-eosin stained preparation, 430x. A. Non-infected Hep-2 cell control culture. B. Hep-2 cells infected with adenovirus type 2. (Note: intranuclear inclusions, arrows) and parainfluenza virus type 5 (Note: multinucleated cells, double arrows).

TABLE IV

Herpesviruses of Man

Virus serotype	Cell culture system				Mouse Pathogenicity	Embryonated Egg
	RhMK	WI-38	Hep-2	RK		
Herpes simplex virus types 1 and 2	±[1]	+	+	+	+	+[2]
Cytomegalovirus	–	+	–	–	–	–
Varicella-Zoster virus	–	+	–	–	–	–
Epstein-Barr virus	–	–	–	–	–	–

[1] Footnote 1, see TABLE II

[2] Pock formation on chorioallantoic membrane

tion, since human adenoviruses generally do not replicate in monkey cells. Identification of the adenovirus was made by inhibition of CPE in Hep-2 cell cultures; whereas inhibition of hemadsorption in monkey cell cultures was used for identifying the parainfluenza virus.

The Herpesviruses

These are large size, 110–150 nm in diameter, acid-labile, DNA-containing viruses. They are surrounded by a lipid-containing envelope and are sensitive to ether treatment. Herpes simplex types 1 and 2, cytomegalovirus (CMV), varicella-zoster (V-Z), and Epstein-Barr (EB) virus infect man (Table IV).

The most striking characteristic of herpesvirus infection in man is its propensity for persistence in a latent state with recurrence of its activity at irregular intervals. The ability of the herpesvirus to establish latent infection and the association of herpes simplex type 2 and the EB virus as etiologic agents for human cancer have stimulated much interest in recognition and isolation of viruses in this group.

Herpes simplex virus type 1

Infection with herpes simplex virus (HSV) type 1 is widespread and usually asymptomatic (60). The most common age for primary infection is from 2–4 years as in the case of acute gingivostomatitis. Primary infections may also involve the eye and central nervous system. Recurrent herpes simplex represents activation of a latent infection normally referred to as cold sores. The recent finding that HSV can be recovered from human trigeminal ganglia obtained at autopsy using cocultivation techniques (61) has given considerable impetus to the investigation of this virus in clinical virology.

The herpes simplex virus has a wide host range both in animals and in cell culture systems. In addition to human cells, non-human cells, especially rabbit kidney, are highly sensitive to HSV infection (Figure 7B). Typical cowdry type A intranculear inclusions are easily obtained (Figure 7D). Because of the wide host spectrum, presumptive diagnosis of HSV infection can at times be made within 24 hours on the basis of the distinctive CPE in primary rabbit kidney cells in which other members of the herpes group do not grow (Table IV). Presumptive identification also can be made by looking for typical tiny pocks which appear on the chorioallantoic membrane of embryonated eggs. Final identification requires neutralization test in tissue culture, either by inhibition of CPE or plaque reduction, using type-specific serum.

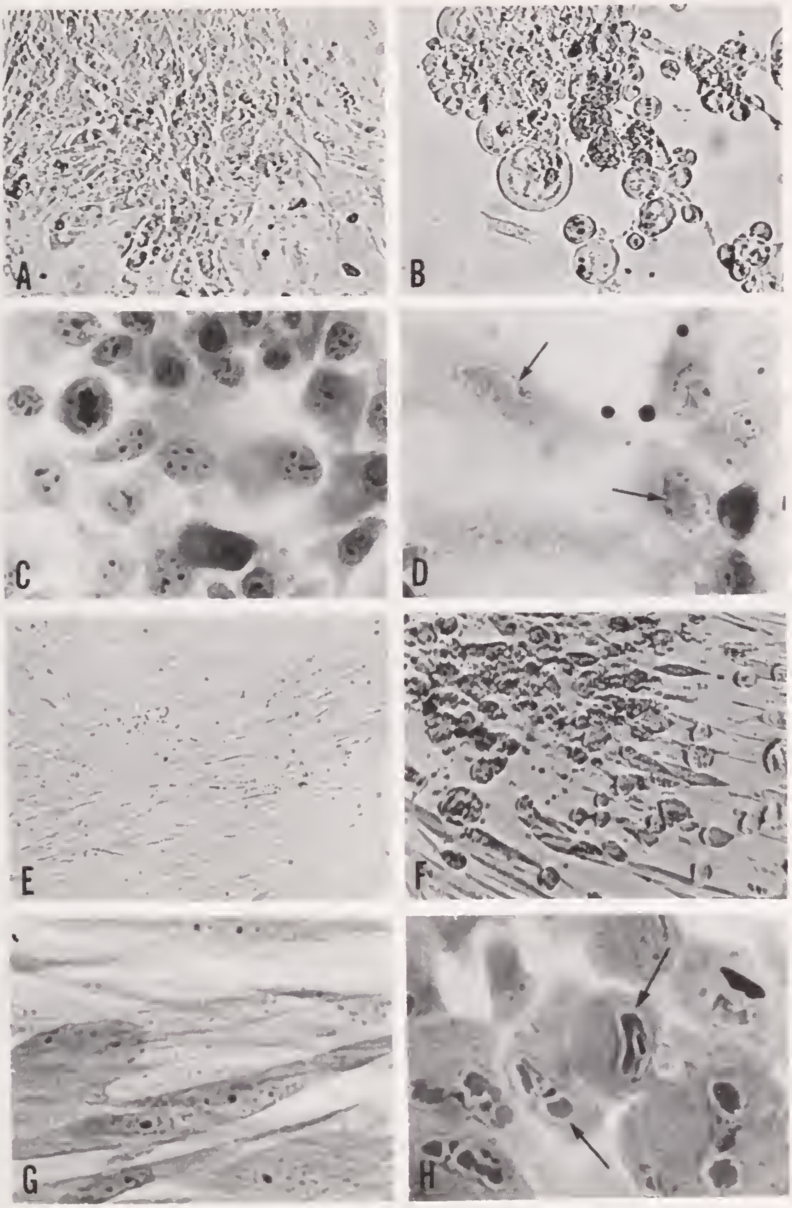

FIG. 7. Herpesvirus induced CPE and inclusions in different cell systems, A, B, E and F, 100×; C, D, G and H, hematoxylin-eosin stained preparation, 430×. A. Non-infected rabbit kidney cell culture; B. CPE induced by HSV-1 in rabbit kidney cells; C. Non-infected Hep-2 cell culture; D. Intranuclear inclusions induced by HSV-1 (arrows); E. & G. Non-infected WI-38 cell culture; F. CPE induced by CMV in WI-38 cells; H. Intranuclear inclusion induced by CMV in WI-38 cells (arrows).

Herpes simples virus type 2

The herpesvirus strains isolated from the genital tract are known as HSV type 2 and are different both antigenically and biologically from the HSV type 1 strains isolated from oral, skin or neurologic lesions. Since cytopathic effect and host range of HSV type 2 closely resemble that of HSV type 1, serologic test and determination of other biologic properties are necessary to distinguish between the two virus types.

Human cytomegalovirus (CMV)

Neonatal CMV infection is usually congenital and results in generalized, often fatal cytomegalic inclusion disease (62). Patients with malignancies or antibody deficiencies or those undergoing immunosuppressive therapy for organ transplantation may develop a generalized cytomegalovirus infection which is characterized by virus excretion in the urine in the presence of significant antibody levels for prolonged periods of time. The most sensitive cell system for isolation of CMV is human fibroblast, for example WI-38. Since CMV is relatively unstable, it is important to inoculate infected urine, or other specimens, into test cultures without prior feezing. For biopsy specimens or autopsy tissues, cultivation or cocultivation with human fibroblast cell monolayers of trypsin dispersed infected cells offers greater sensitivity than procedures for virus isolation utilizing tissue homogenates. Occasionally secondary passage, by trypsin-dispersal of cultivated infected cells, followed by 2–3 months observation may be necessary to establish virus infection. The development of focal CPE in fibroblasts is typical of CMV cytopathology and its spread is usually very slow (Figure 7F). Following hematoxylin-eosin staining, eosinophilic intranuclear inclusions are easily observed (Figure 7H). The characteristic CMV inclusions are pathognomonic for this virus type and usually can be used for the differentiation of CMV from other members of the herpesvirus group. Final identification can be made by complement-fixation or neutralization tests.

Varicella-zoster virus (V-Z virus)

Varicella, or chicken pox virus infection commonly occurs in childhood whereas zoster virus disease is mainly observed in adults. According to all laboratory tests, chicken pox and zoster are caused by the same agent. Laboratory diagnosis is rarely performed since the clinical picture is so characteristic. Unlike herpes simplex virus, V-Z virus has an extremely narrow host range and infects only man and in tissue culture infects only human cells. Unlike CMV, V-Z virus prefers epithelial cells in culture. CPE appears in foci and spreads slowly. In addition, subculture of V-Z virus requires passage of viable infected cells (29, 63).

Epstein-Barr herpesvirus

The observation of a herpes-like virus, subsequently named EB virus, in cultured lymphoblasts derived from Burkitt's lymphomas by Epstein et al. in

1964 (41) opened a new area of interest in clinical virology. The relationship of EB virus to the development of lymphoproliferative diseases has been a primary subject in the study of human cancer (64). Primary infection with EB virus may occur in early childhood without any clinical manifestation but infection of young adults results in infectious mononucleosis (65). Evidence of prolonged excretion of EB virus in the oropharyngeal secretions of patients with infectious mononucleosis was demonstrated following inoculation of human cord blood cell suspensions with specimens from these patients (66). The presence of the EB virus in the pharyngeal swabs or throat washings was determined by observation of clumping of the cord blood cells. The latter was prevented by using sera from patients recovering from infectious mononucleosis. However, fluorescent antibody techniques using known cell lines carrying EB virus and complement-fixation tests are the most common practical procedures available for serologic diagnosis. Although EB virus has been given much attention in research on viral oncology, its role in clinical virology has yet to be fully explored.

SUMMARY

As with other laboratory tests in the clinical laboratory, it is necessary to interpret the test results of virus studies in relation to the illness of the patient. It must be borne in mind that isolation of any agent, accompanied by a demonstration of rise in specific antibody, does not necessarily mean that the isolate is the etiologic agent for the current disease. Thus while much can be contributed to the diagnosis of an infection by laboratory studies, this information must be evaluated together with the patient's clinical history before a specific virus can be designated as the etiological agent of the disease.

Sufficient laboratory testing procedures are now available to provide rapid and accurate diagnosis of most of the common viral infections. With the commercial availability of various cell cultures and standard reagents, isolation and identification of the more common viral agents can be easily accomplished in a routine clinical virology laboratory in a manner similar to those services provided by a bacteriology laboratory. Through the application of these procedures, a number of other services to the patient and medical staff can be confirmed. For example, one can (i) prevent the unnecessary use of antibacterial drugs, (ii) furnish a more accurate prognosis and thus enhance the physician's clinical acumen, and (iii) provide timely detection of outbreak of a viral epidemic and thus permit the timely application of proper public health measures. Furthermore, some antiviral drugs are now available and there is every possibility that more will exist in the future. For the treatment of certain viral diseases the establishment of a laboratory diagnosis is essential for the selection of proper chemotherapy.

Recently the application of immune electron microscopy has led to the recognition of many viruses with a hitherto unknown association with any clinical disease. The isolation of slow viruses from the central nervous system through the use of cultivation and cocultivation techniques has reinforced the importance of clinical virology in modern medicine. With the present increased interest in the development of various virological techniques in clinical medicine, it is anticipated that the services of the diagnostic virology laboratory will undoubtedly be increased and further utilized in the very near future.

References

1. Hsiung, G. D., Pinheiro, F., and Gabrielson, M. O.: The Virus Diagnostic Laboratory: Functions and Problems Based on Three Years' Experience, Yale J Biol Med 36:104–123, 1963.
2. Horstmann, D. M. and Hsiung, G. D.: Principles of Diagnostic Virology. In *Viral and Rickettsial Infections in Man*, 4th ed., Edited by F. L. Horsfall, Jr. and I. Tamm. J. B. Lippincott, Philadelphia 1965, pp. 405–424.
3. Russell, W. O.: Introduction, 6th Annual ASCP Research Symposium. Laboratory Diagnosis of Viral Infections: Recent Advances and Their Clinical Application, Am J Clin Pathol 57:731–732, 1972.
4. Herrmann, E. C., Jr.: New Concepts and Developments in Applied Diagnostic Virology, Progr Med Virol 17:221–289, 1974.
5. Lennette, E. H. and Schmidt, N. J.: *Diagnostic Procedures for Viral Rickettsial Infections*, 4th ed., American Public Health Association, Inc., New York 1969.
6. Hsiung, G. D.: *Diagnostic Virology. An Illustrated Handbook*, Yale University Press, New Haven 1973.
7. The Use of Electron Microscopy in Diagnostic Virology, Convener: G. D. Hsiung, Am Society Microbiology Annual Meeting, Miami 1973.
8. Hsiung, G. D.: Further Studies on Characterization and Grouping of ECHO Viruses—Comparative Virology, Ann NY Acad Sci 101:413–422, 1962.
9. Gabrielson, M. O. and Hsiung, G. D.: Sensitivity of Agar Overlay Method for the Recognition of Enteroviruses, Appl Microbiol 13:967–972, 1965.
10. Hull, R. N.: The Simian Viruses, Virology Monographs 2:1–66, 1968.
11. Hsiung, G. D.: Latent Virus Infections in Primate Tissues with Special Reference to Simian Viruses. Bact Rev 32:185–205, 1968.
12. Smith, K. O.: Adventitious Viruses in Cell Cultures, Progr Med Virol 12:302–336, 1970.
13. Swack, N. S. and Hsiung, G. D.: Endogenous Agents in Primary Cell Cultures, In Vitro 10:260–267, 1974.
14. Stanbridge, E.: Mycoplasmas and Cell Cultures, Bact Rev 35:206–227, 1971.
15. Barile, M. F.: Mycoplasmal Contamination of Cell cultures: Mycoplasma-Virus-Cell Culture Interactions. In *Contamination in Tissue Culture*, Edited by J. Fogh. Academic Press 1973, pp. 131–172.
16. Coleman, M. T. and Dowdle, W. R.: Properties of the Hong Kong Influenza Virus. I. General Characteristics of the Hong Kong Virus, Bull WHO 41:415–418, 1969.
17. Sever, J. L.: Application of Microtechnique to Viral Serological Investigations, J Immunol 88:320–329, 1962.
18. Kriel, R. L., Wulff, H., and Chin, T. D. Y.: Microneutralization Test for Determination of Rhinovirus and Coxsackievirus A Antibody in Human Diploid Cells, Appl Microbiol 17:611–613, 1969.
19. Person, D. A. and Herrmann, E. C., Jr.: Laboratory Diagnosis of Rubella Virus Infections and Antibody Determinations in Routine Medical Practice, Mayo Clin Proc 46:477–483, 1971.
20. Liu, C.: Rapid Diagnosis of Human Influenza Infection from Nasal Smears by Means of Fluorescein-Labeled Antibody. Proc Soc Exp Biol Med 92:883–887, 1956.
21. Liu, C.: Diagnosis of Influenza Infection by Means of Fluorescent Antibody Staining, Am Rev Resp Dis 83:130–133, 1961.
22. Sommerville, R. G.: Rapid Identification of Neurotropic Viruses by Immunofluorescent Technique Applied to Cerebrospinal Fluid Cellular Deposits, Arch Gesamte Virusforch 19:63–69, 1966.

23. Sommerville, R. G.: Rapid Diagnosis of Viral Infections by Immuno-fluorescent Staining of Viral Antigens in Leucocytes and Macrophages, Progr Med Virol 10:398–414, 1968.
24. Henle, G. and Henle, W.: Immunofluorescence in Cells Derived from Burkitt's Lymphoma, J Bacteriol 91:1248–1256, 1966.
25. Johnson, H. N.: Rabiesvirus. In *Diagnostic Procedures for Viral and Rickettsial Infections,* 4th ed., Edited by E. H. Lennette and N. J. Schmidt. American Public Health Association, Inc., New York 1969, pp. 321–353.
26. Blumberg, B. S., Byrne, R. J., Chanock, R. M., Cockburn, W. C., Kono, Y., Koza, J., McCollum, R. W., Menache, D., Penttinen, K., Purcell, R. H., Taylor, P. E., Wewalka, F. G., and Zuckerman, A. J.: Viral Hepatitis and Tests for Australia (Hepatitis-Associated) Antigen and Antibody, Bull WHO 42:957–992, 1970.
27. LeBouvier, G. L., and McCollum, R. W.: Australia (Hepatitis-Associated) Antigen: Physiochemical and Immunological Characteristics, Adv Virus Res 16:357–396, 1970.
28. Rowe, W. P., Huebner, R. J., Gilmore, L. K., Parrott, R. H., and Ward, T. G.: Isolation of a Cytopathogenic agent from human Adenoids Undergoing Spontaneous Degeneration in Tissue Culture, Proc Soc Exp Biol Med 84:570– 573, 1953.
29. Weller, T. H.: Serial Propagation in Vitro of Agents Producing Inclusion Bodies Derived from Varicella and Herpes Zoster, Proc Soc Exp Biol Med 83:340–346, 1953.
30. Horta-Barbosa, L., Fuccillo, D. A., Sever, J. L., Zeman, W.: Sub-Acute Sclerosing Panencephalitis: Isolation of Measles Virus from a Brain Biopsy, Nature 221:974, 1974. 1969.
31. Payne, F. E., Baublis, J. V., and Itabashi, H. H.: Isolation of Measles Virus from Cell Cultures of Brain from a Patient with Subacute Sclerosing Panencephalitis, New Engl J Med 281:585–589, 1969.
32. Weiner, L. P., Herndon, R. M., Narayan, O., Johnson, R. T., Shah, K., Rubinstein, L. J., Preziosi, T. J., and Conley, F. K.: Isolation of Virus Related to SV40 from Patients with Progressive Multifocal Leukoencephalopathy, New Engl J Med 286:385–390, 1972.
33. Padgett, B. L., Walker, D. L., ZuRhein, G. M., Eckroade, R. J., and Dessel, B. H.: Cultivation of Papova-Like Virus from Human Brain with Progressive Multifocal Leucoencephalopathy, Lancet 1:1257–1260, 1971.
34. Tyrrell, D. A. J.: Rhinoviruses, Virology Monographs 2:67–124, 1968.
35. McIntosh, K., Dees, J. H., Becker, W. B., Kapikian, A. Z., and Chanock, R. M.: Recovery in Tracheal Organ Cultures of Novel Virus from Patients with Respiratory Disease, Proc Nat Acad Sci USA 57:933–940, 1967.
36. Nagler, F. P. O. and Rake, G.: The Use of the Electron Microscope in Diagnosis of Variola, Vaccinia, and Varicella, J Bacteriol 55:45–51, 1948.
37. Dane, D. S., Cameron, C. H., and Briggs, M.: Virus-Like Particles in Serum of Patients with Australia-Antigen-Associated Hepatitis, Lancet 1:695–698, 1970.
38. Cruickshank, J. G., Bedson, H. S., and Watson, D. H.: Electron Microscopy in the Rapid Diagnosis of Smallpox, Lancet 2:527–530, 1966.
39. Williams, M. G., Almeida, J. D., and Howatson, A. F.: Electron Microscope Studies on Viral Skin Lesions. A Simple and Rapid Method of Identifying Virus Particles, Arch Dermatol 86:290–297, 1962.
40. Smith, K. O. and Melnick, J. L.: Recognition and Quantitation of Herpesvirus Particles in Human Vesicular Lesions, Science 137:543–544, 1962.
41. Epstein, M. A., Achong, B. G., and Barr, Y. M.: Virus Particles in Cultured Lymphoblasts from Burkitt's Lymphoma, Lancet 1:702–703, 1964.
42. Bunting, H.: Close-Packed Array of Virus-Like Particles within Cells of a Human Skin Papilloma, Proc Soc Exp Biol Med 84:327–332, 1953.
43. ZuRhein, G. M. and Chou, S. M.: Particles Resembling Papova Viruses in Human Cerebral Demyelinating Disease, Science 148:1477–1479, 1965.
44. Kapikian, A. Z., Wyatt, R. G., Dolin, R., Thornhill, T. S., Kalica, A. R., and Chanock, R. M.: Visualization by Immune Electron Microscopy of a 27-nm Particle Associated with Acute Infectious Non-Bacterial Gastroenteritis, J Virol 10:1075–1081, 1972.

45. Feinstone, S. M., Kapikian, A. Z., and Purcell, R. H.: Hepatitis A: Detection by Immune Electron Microscopy of a Virus-Like Antigen Associated with Acute Illness, Science 182:1026–1028, 1973.
46. Bishop, R. F., Davidson, G. P., Holmes, I. H., and Ruck, B. J.: Evidence for Viral Gastroenteritis, New Engl J Med 289:1096–1097, 1973.
47. Flewett, T. H., Bryden, A. S., and Davies, H.: Virus Particles in Gastroenteritis, Lancet 2:1497, 1973.
48. Kapikian, A. Z., Kim, H. W., Wyatt, R. G., Rodriguez, W. J., Cline, W. L. Parrott, R. H., and Chanock, R. M.: Reoviruslike Agent in Stools: Association with Infantile Diarrhea and Development of Serologic Tests, Science 185:1049–1053, 1974.
49. Tamm, I. and Eggers, H. J.: Specific Inhibition of Replication of Animal Viruses, Science 142:24–33, 1963.
50. Mayor, H. D. and Melnick, J. L.: Intracellular and Extracellular Reactions of Viruses with Vital Dyes, Yale J Biol Med 34:340–358, 1961–62.
51. Smith, K. O. and Melnick, J. L.: A Method for Staining Virus Particles and Identifying Their Nucleic Acid Type in the Electron Microscope, Virology 17:480–490, 1962.
52. Hsiung, G. D.: Use of Ultrafiltration for Animal Virus Grouping, Bact Rev 29:477–486, 1965.
53. Committee on the Enteroviruses, National Foundation for Infantile Paralysis. The Enteroviruses, Am J Public Health 47:1556, 1957.
54. Lim, K. A. and Benyesh-Melnick, M.: Typing of Viruses by Combinations of Antiserum Pools. Application to Typing of Enteroviruses (Coxsackie and ECHO), J Immunol 84:309–317, 1960.
55. Schmidt, N. J., Guenther, R. W., and Lennette, E. H.: Typing of ECHO Virus Isolates by Immune Serum Pools. The "intersecting serum scheme," J Immunol 87:623–626, 1961.
56. Kapikian, A. Z., Conant, R. M., Hamparian, V. V., Chanock, R. M., Dick, E. C., Gwaltney, J. M., Jr., Hamre, D., Jordan, W. S., Jr., Kenny, G. E., Lennette, E. H., Melnick, J. L., Mogabgab, W. J., Phillips, C.A., Schieble, J. H., Stott, E. J., and Tyrrell, D. A. J.: A Collaborative Report: Rhinoviruses- Extension of the Numbering System, Virology 43:524–526, 1971.
57. Hirst, G. K.: The Myxovirus Group. In *Viral and Rickettsial Infections in Man*, 4th ed., Edited by F. L. Horsfall, Jr. and I. Tamm, J. B. Lippincott, Philadelphia 1965, pp. 685–688.
58. Melnick, J. L.: Classification and Nomenclature of Viruses, Progr Med Virol 17:290–294, 1974.
59. Ginsberg, H. S.: Adenoviruses, Am J Clin Pathol 57:771–776, 1972.
60. Nahmias, A. J., and Roizman, B.: Infection with Herpes-Simplex Viruses 1 and 2. New Engl J Med (Part 1) 289:667–674, 1973. (Part 2) 289:719–725, 1973. (Part 3) 289:781–789, 1973.
61. Baringer, J. R., and Swoveland, P.: Recovery of Herpes-Simplex Virus from Human Trigeminal Ganglions, New Engl J Med 288:648–650, 1973.
62. Weller, T. H.: The Cytomegalovirus: Ubiquitous Agents with Protean Clinical Manifestations, New Engl J Med 285:203–214, 267–274, 1971
63. Weller, T. H., Witton, H. M., and Bell, E. J.: The Etiologic Agents of Varicella and Herpes Zoster. Isolation, Propagation, and Cultural Characteristics *in vitro*, J Exp Med 108:843–868, 1958.
64. Biggs, P. M., de-Thé, G., and Payne, L. N.: *Oncogenesis and Herpes Viruses*, International Agency for Research on Cancer, Lyon 1972.
65. Henle, G., Henle, W., and Diehl, V.: Relation of Burkitt's Tumor-Associated Herpes-Type Virus to Infectious Mononucleosis, Proc Natl Acad Sci USA 59:94–101, 1968.
66. Miller, G., Niederman, J. C., and Andrews, L. L.: Prolonged Oropharyngeal Excretion of Epstein-Barr Virus after Infectious Mononucleosis, New Engl J Med 288:229–232, 1973.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 43, No. 6, November December, 1976
Printed in U.S.A.

Cultivation of Entamoeba histolytica as a Diagnostic Procedure: A Brief Review

MORTON H. EDELMAN, M.D. AND CLIFFORD L. SPINGARN, M.D.

We have been asked to contribute a publication in honor of Doctor Stanley S. Schneierson to whom this volume is dedicated. It is a particular satisfaction for us to add to the general expression of appreciation to a physician and scientist who is outstanding in the field of microbiology and medicine. Although he is well known for his work in diagnostic bacteriology, he has made equally singular contributions in parasitology, demonstrating a wide experience with the morphologic and staining characteristics of the individual helminths and protozoa in preparations from specimens of patients in the hospital. With the collected material, he included excellent color photographs of the major parasites of man in a laboratory manual written primarily for teaching of medical students and others interested in this specialty (1).

When Doctor Schneierson returned from Navy Service in World War II, the authors had both returned from the South Pacific theater. Doctor Schneierson guided us in the establishment of the parasitology section of Mount Sinai's microbiology division which at that time was under the direction of Doctor Gregory Shwartzman. We had regular seminars in Doctor Shwartzman's office and interesting patient material was presented with a detailed description of the organisms which had been isolated. During the years that followed, Doctor Schneierson continued to assist us and guide us in the parasitology laboratory and in our research, giving unstintingly of his time and talents.

One important phase of our research activities was our interest in perfecting a useful and simple method for the isolation and positive identification of Entamoeba histolytica by cultivation. A number of publications reported these studies over the years (2–7). Our experiences suggested to us a need for a method which would favor growth of amebic trophozoites from cysts because in temperate climates it is this stage of the protozoa which is most often present in routine fecal specimens. The other usual routine methods of diagnosis available for the laboratory diagnosis of amebiasis appeared to have certain shortcomings in our hands.

Amebiasis was an endemic infection in the Southwest Pacific during World War II; there the clinical picture was usually a fullblown acute dysenteric colitis. Under these circumstances, in an army hospital laboratory in the Philippines, trophozoites were identified easily in the microscopic sections of unstained fecal material, often in large enough numbers to be impressive.

From the Departments of Microbiology and of Medicine, The Mount Sinai Hospital, New York, N. Y. 10029.

Requests for reprints should be sent to: Dr. Morton H. Edelman, Department of Medicine, The Mount Sinai Hospital, Fifth Avenue and 100 Street, New York, N. Y. 10029.

Time and other responsibilities did not allow laboratory investigation of the more inactive stages of the infection, and these individuals usually were not hospitalized.

In returning to a hospital setting in a temperate climate, however, it was found that the acute stages of amebic colitis were infrequently seen and low-grade disease was the usual clinical state. The requirement for an accurate diagnosis was either to search for trophozoites in the stool after saline cathartics, or to detect the cyst in a smear from a casual specimen by direct examination, or after concentration with zinc sulfate or acid-ether and both in the unstained and stained preparations. If available, a fixed stain with trichrome or iron hematoxylin could be used for further identification and permanent sections.

We concluded from our experiences in the laboratory that positive identification of the amebic cyst was not always simple. The time consumed in locating and identifying a small number of cysts could be disturbing. When found, the E. histolytica cyst might stain poorly with iodine or be distorted by the concentration technique making identification difficult. In addition, the cyst is small, average 10 microns, slightly larger than a red blood cell. The eyes have to be trained to find these organisms under the low power of the microscope. It took the authors several years before they considered themselves expert in identifying E. histolytica cysts in fecal smears. The iron hematoxylin fixed stains require special experience and are time-consuming, and similar difficulties with identification occur. It is likely that other laboratories have become expert in these other methods and rely on them completely. However, in a busy hospital treating a wide range of illnesses, time in the laboratories is often divided into the performance of many duties, and this applies to the parasitology laboratory as well.

We have found it very helpful, under these circumstances, to add cultivation to our diagnostic armamentarium, using liver infusion agar, a laboratory procedure that has been carried out for many years. Our original investigations helped to improve the culture media we selected by adding antibiotic to the culture. This prevented bacterial overgrowth and prolonged the survival of trophozoites when grown from cysts. In addition, we established a fixed amount of rice powder (50 mg per tube) that would be most favorable for initiation and growth of the E. histolytica. We studied also the relationship of the number of cysts in the emulsion cultured to the likelihood of growth of trophozoites.

The culture method developed in our laboratory and used in the routine diagnosis for identification of E. histolytica was first described by Cleveland and Sanders (8) and Cleveland and Collier (9) in 1930. They found the media "virtually specific for E. histolytica." In their experiments, E. coli, the most common ameba of man, failed to grow on repeated attempts. This feature of species specificity with this media can be of great importance in differential diagnosis of the amebae of man, and its value has not been generally appreciated. In addition, the media allows the E. histolytica to initiate growth from the cyst stage which has been an advantage when dealing with the light infections or negative smears from which neither trophozoites nor cysts can be detected.

The diphasic culture medium of Cleveland and Collier used in our laboratory is prepared by the Difco Laboratories and consists of a liver infusion agar solid slant and a serum-saline overlay (dilution 1:6) into which 50 mg of sterile rice powder is added. Six tubes are prepared for each culture, of which two are controls. In the other four tubes antibiotic is added to prevent bacterial overgrowth in the following concentrations, 3 mg and 6 mg of streptomycin in tubes one and two, and 3000 and 6000 units of penicillin in tubes three and four, respectively. Material from the liquid phase of the culture is examined microscopically every twenty-four hours for a total of seven days, after incubation at 37 degrees centigrade. Identification of the trophozoites of E. histolytica is made by expert familiarity with the characteristic morphology and motility. The trophozoites multiply and the diagnosis is facilitated by the abundance of the motile forms found. The culture can be maintained for long periods of time by subculturing. In contrast, E. coli, when developed in culture, occasionally, shows sluggish motility, other morphologic differences from the E. histolytica, and has not been maintained in culture more than two weeks (10). In our experience the growth of E. coli in our cultures has been evanescent. E. histolytica cysts, when found prior to cultivation, are studied for their size (average 10 microns), staining characteristics (at times take the stain poorly with Lugol's or D'Antoni's solution), and the number of nuclei present (one to four). We have recorded routinely cyst counts either counting all the cysts in a properly prepared smear when there are smaller numbers, or estimating them when there are more than 100 cysts per smear. The great majority of specimens in this group, with chronic asymptomatic or nondysenteric amebiasis, show cysts in the number of three to fifty per smear, unconcentrated. The most common average group were those unconcentrated smears which showed in the range of ten to twenty cysts per smear. These will excyst in the culture tubes in 24 to 72 hours or longer and then can be maintained by subculturing. We have maintained viable cultures in this way for many months. Infrequently, the culture is not maintained and dies off in several weeks. The explanation for this is not known but possibly could be due to strain variations or bacterial interactions. The use of antibiotics in the culture media, either penicillin or streptomycin, reduces the overgrowth of intestinal flora which unless controlled in this way would be inimical to the maintenance of the viability of the culture.

It has been stated that the differentiation of trophozoites of E. histolytica and E. coli is difficult possibly more so in culture than when studied directly from the stool. Our conclusion that we are dealing with the histolytica species in the culture which grows out is based, therefore, on the following considerations: 1) the liver infusion agar medium of Cleveland and Collier is generally specific for E. histolytica. In the rare instance in which E. coli does grow out in culture, it is not maintained and dies off quickly; 2) identification of cysts is made prior to cultivation and when E. coli is present alone, positive cultivation usually does not occur; and 3) the characteristics of the trophozoites of E. histolytica in culture are distinctive; the pseudopodial activity, morphology, and prolonged viability are unmistakable.

In a report of a clinical seminar on amebiasis, William A. Sodeman (11) said that "an exhaustive re-evaluation of the efficiency of cultural methods for the diagnosis of amoebic infection is required." Further he stated "that we are currently no more justified in accepting the microscopic examination of the stool for the diagnosis of E. histolytica than we would be in restricting ourselves solely to the gram stain of sputum smear for the diagnosis of pneumonia." In this regard, the Laredo-like strain of E. histolytica, which is nonpathogenic, can be excluded from the diagnosis if the biologic characteristics in the culture are studied. Failure of the culture to grow in low temperature (25–30 degrees centigrade) excludes the Laredo-like strain. Examining the cyst or trophozoites alone without the culture could not make this differentiation.

It has been our experience with a small number of specimens studied of the small race of E. histolytica (E. hartmanni) measuring an average of 8 microns or less, that growth in the Cleveland Collier media does not occur. This is too small a series to allow us to reach a positive conclusion that the small race of E. histolytica fails to grow in this media. But if it can be confirmed with a larger series, it is an additional means of excluding this nonpathogenic species as the causative agent in clinical amebic disease. Others have reported growth of E. hartmanni using other types of media. Methods of separating these three species known to occur in man would assist greatly in reaching a definitive diagnosis of clinical amebiasis. Neal (12) summarizes this classification as follows:

1. Small race (E. hartmanni) based on size and absence of virulence.
2. E. histolytica-like (Laredo type) indistinguishable from E. histolytica but growing at temperatures below 37 degrees centigrade (optimum temperature 26 degrees centigrade).
3. Large race E. histolytica—the only amebae responsible for invading tissue in man.

It is also of interest that Robinson (13) in England, who has been a strong advocate of cultivation methods in amebiasis, stated that "classical techniques for amoebae were not suited to the clinical laboratory so that simpler methods had to be devised as we went along." And further, he stated, "a special feature has been the extensive culturing of amoebae from human feces." Dr. Robinson also stated that cyst identification may be more difficult for the inexperienced observer than the identification of trophozoites in culture. We concur in this, since the trophozoite is larger, more distinctive, and often more abundant in culture. He demonstrates his understanding of the problem and agrees with our experiences when he states so pointedly, "more often than one cares to admit has an actual dysentery patient been diagnosed by the 48-hour culture reading before a) the ward has been persuaded to send a fresh (instead of ancient) specimen and b) the right pair of eyes to find one indolent trophozoite in 20 high-powered fields has been brought to the microscope." In Robinson's series, using a different media with added erythromycin, cultures were obtained from all the E. histolytica positive fecal specimens, while 2.8% were missed microscopically. He found that a significant number of positive cultivations for E. histolytica were obtained in fecal specimens microscopically negative or containing only nonhistolytica species. This agrees with our experience in finding occasionally successful positive cultivation of E. histolytica in microscopically negative smears for cysts.

Kudo (14), in his textbook on protozoology, stated "that protozoa should be studied as far as possible in life. Permanent preparations while indispensible in revealing many intracellular structures cannot replace fresh preparations." Burrows (15) recommended that a media be selected in the laboratory and used frequently enough to allow for development of a skill with that particular method. Technicians who have cultured fecal specimens for amebae routinely have found the procedure simple, effective, time-saving and accurate.

Summary

1) Many methods are available for use in the laboratory diagnosis of amebic infection from fecal specimens. These include search for the trophozoites of E. histolytica after purging, direct smear examination of fecal material in casual specimens, unstained or stained with various iodine preparations, concentration techniques using zinc sulfate flotation, or acid-ether and the preparation of fixed smears with trichrome stain or iron hematoxylin. All of these require special training and much of it is time-consuming, possibly to the point of being inefficient.

2) In endemic amebiasis or in acute explosive amebic colitis, trophozoites may be identified with ease. However, the more chronic and asymptomatic phases of this infection are characterized by a paucity of amebic cysts in the stool which may be missed or if found not be morphologically distinctive. Here too special technical skill is required which may not be available and a prolonged period of time is often required to make certain that the small cysts are not missed.

3) Cultivation of fecal material for the isolation and growth of E. histolytica can be carried out successfully with the differential media devised by Cleveland and Collier and used in our laboratory for many years. The E. histolytica are easily identifiable by their motility, morphology, luxuriance in culture, and the prolonged survival when subcultured. This method is of special value either to confirm a suspected positive microscopic diagnosis of E. histolytica or to isolate the organism when it has failed to be detected in the specimens studied by all other laboratory techniques. In addition, it may be possible to identify in culture the Laredo-like stain which is non-pathogenic and which grows only at low temperatures (optimum 26 degrees centigrade) and to confirm the finding of the small race histolytica (E. hartmanni) by its failure to grow in this media when cultured from the cyst stage.

4) Finally, and not the least important, the total time involved in preparing the culture and checking the results microscopically is much less than the time required for study of direct smears, concentration techniques, and staining methods, singly or combined, especially in chronic asymptomatic amebiasis with the passage of small numbers of cysts.

References

1. Schneierson, S. Stanley: *Atlas of Diagnostic Microbiology*. Abbott Laboratories, N. Chicago, Illinois.
2. Spingarn, C. L. and Edelman, M. H.: The Prolongation of the Viability of Cultures of E. hystolytica by the Addition of Streptomycin, J Parasitol 33:5:416–418, 1947.
3. Spingarn, C. L. and Edelman, M. H.: The Use of Streptomycin in the Cultivation of Endamoeba histolytica from Stools, Am J Trop Med 28:825–829, 1948.
4. Spingarn, C. L. and Edelman, M. H.: The Effect of Rice Powder on the Growth of Cultures of Endamoeba histolytica, Am J Trop Medi 30:629–634, 1950.
5. Spingarn, C. L. and Edelman, M. H.: The Effect of Aureomycin Hydrochloride on the Growth of Endamoeba histolytica in Vitro, Am J Trop Med 31:206–211, 1951.
6. Spingarn, C. L. and Edelman, M. H.: Further Observations on the Use of Streptomycin and Penicillin in the Cultivation of Endamoeba histolytica from Stools, Am J Trop Med Hyg 1:412–416, 1952.
7. Edelman, M. H. and Spingarn, C. L.: The Relation of the Number of Cysts in the Stool Inoculum to the Incidence of Positive Cultures of Endamoeba histolytica, Am J Trop-Medi 3:995-998, 1954.
8. Cleveland, L. R. and Sanders, E. P.: Encystation, Multiple Fission without Encystment, Excystation, Metacystic Development, and Variation in a Pure Line, and in Nine Strains of Entamoeba histolytica, Arch f Protistenk 70:223–266, 1930.
9. Cleveland, L. R. and Collier, J.: Various Improvements in the Cultivation of Entamoeba histolytica, Am J Hyg 12:606-613, 1930.
10. Wittner, M.: Personal Communication.
11. Sodeman, W. A.: Clinical Seminar: Amoebiasis, Am J Dig Dis 16:51–60, 1971.
12. Neal, R. A.: Pathogenesis of Amoebiasis, Gut 12:9483–9486, 1971.
13. Robinson, G. L.: The Laboratory Diagnosis of Human Parasitic Amoebae, Trans Roy Soc Trop Med Hyg 62:285–294, 1968.
14. Kudo, R. S.: *Protozoology*, 5th. Edition, 1971, p. 1076.
15. Burrows, R.B.: *Microscopic Diagnosis of the Parasites of Man*. Yale University Press: 1965, p. 60.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 43, No. 6, November-December, 1976
Printed in U.S.A.

Bacterial Toxins as Virulence Factors: Shiga Bacillus Dysentery Viewed as a Toxinosis*

GERALD T. KEUSCH, M.D.

Mechanisms of bacterial virulence are of interest to the medical scientist and clinician alike, as problems for basic research and as clues to a rational approach to disease. In this context, no mechanism is more germane than the effects of bacterial toxins. For example, the exotoxin of V. cholerae is being intensively studied by the biochemist and physiologist to determine its mechanism of action and by the clinician trying to treat the disease it causes through rational pharmacology. Furthermore, efforts are being expended to develop a toxoid vaccine to use for prophylactic immunization. It is somewhat surprising that more than 80 years after the discovery of diphtheria toxin and the development of diphtheria toxoid the nature and importance of bacterial toxins is still poorly understood by physicians. This paper will attempt to clarify some important basic premises about toxins as virulence factors using as an example one of the older, and at the same time, newer known toxins, that of S. dysenteriae 1 (Shiga's bacillus).

Definitions

What is a toxin and how are toxins classified? The medical dictionary defines a toxin as a poisonous material of microbial, vegetable or animal origin (1). This serves to differentiate molecules which cause structural damage or functional abnormalities by virtue of their chemical action into toxins, when of organic origin, and poisons when not. Both toxins and poisons are thus viewed as "toxic" and "poisonous" substances. That this is not necessarily the case is clearly indicated by the action of V. cholerae exotoxin which does not cause structural abnormalities but rather turns on a normal secretory process via a normal mechanism in the intestinal epithelial cell (2). The structural and functional damage which occurs in cholera is instead a secondary phenomenon due to fluid loss, acidosis and shock. Cholera as a toxinosis is a disease of excess, too much of a normal event which is self-limited in time so long as the toxin is present to affect the gut mucosa. Toxins, then, are molecules produced by living cells with biological activity (either destructive or stimulatory) which results in disease symptoms in the host.

From the Department of Medicine, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

* These studies have been supported by Contract DADA-17-C-1042 from the U.S. Army Medical Research and Development Command. Dr. Keusch was the recipient of Career Scientist Award I-767 from the Health Research Council of the City of New York during a portion of these studies and currently is supported by a Research Career Development Award (-04-AI-70847) from the National Institute of Allergy and Infectious Disease.

Requests for reprints should be sent to: Dr. Gerald Keusch, Mount Sinai School of Medicine, Fifth Avenue and 100 Street, New York, N. Y. 10029.

A second major criterion defining toxins which is generally accepted is that these molecules are proteins, whether simple or complex (3). Thus bacterial cell wall lipopolysaccharide, also called endotoxin, is not a true toxin at all. One reason for this distinction is that toxins, as proteins, are antigenic and thus can stimulate production of neutralizing antibodies capable of protecting against the disease symptoms they mediate, e.g., tetanus and diphtheria. Lipopolysaccharide, while of organic origin and biologically active, may be detoxified by non-immune mechanisms (4).

A further distinction between the protein toxins and lipopolysaccharide is that the former have specific biochemical actions or enzymatic activity whereas the latter acts "non-specifically." Thus, theoretically, specific pharmacologic mediation of toxin action is possible whereas lipopolysaccharide may affect many different cell processes simultaneously. Restriction of the term bacterial toxin to biologically active proteins of microbial origin does not mean, however, that bacteria do not produce low molecular weight, non-protein, toxic substances.

Reference to lipopolysaccharide as endotoxin to distinguish this material from protein exotoxins, such as botulinus exotoxin, uses the bacterial cell as a geographic frame of reference. Toxic materials associated with the bacterial cells are called endotoxins, whereas exotoxins are released into the extracellular medium. However this differentiation is highly artificial, and depends upon conditions of bacterial growth, time of sampling and the particular toxin in question. For example many protein toxins are found in highest concentration within the bacterial cell early in the growth cycle of the organism, whereas with time in culture bacterial lysis occurs and free lipopolysaccharide may be found in the extracellular milieu. It is not possible to remove by fiat, however compelling the logic, terms so firmly fixed in the medical literature such as *endotoxin* and *exotoxin*. As a distinction of chemical nature rather than anatomic localization there is a potential use in retaining the terms. However, the recent explosive advance in knowledge of diarrhea-producing protein "enterotoxins and the frequent confusion between entero- and endotoxin, indicates that the terms endo- and exotoxins have indeed outlived their historical value—they now contribute more to confusion than understanding. A conscious effort to speak only of lipopolysaccharide and of protein toxins and to exorcise the endo- and exo- classification is not only indicated, but may be the only way to accomplish this change.

A problem remains, however, in nomenclature of bacterial protein toxins. How does one classify individual toxins, particularly when one organism produces a multiplicity of such proteins? Description of these substances in terms of their physiological role, e.g., enterotoxin, is one possibility. A nonphysiological listing by number or alphabet (somehow always more impressive when in Greek), e.g., staphylococcal α-toxin, is another. For most toxins physiologic classification is still extraordinarily rudimentary. Both V. cholerae and S. aureus produce "enterotoxins," however the former stimulates the secretory mechanisms of the intestinal epithelial cell ("the enteron") whereas the latter works primarily on the autonomic nervous system (5). Yet they are both called enterotoxins because gastrointestinal symptoms of one sort or another are the major clinical symptoms of the disease. Ultimately, it may be possible to refine the classification system to one based on a precise, concise description of the actual biochemical effect of the toxin, e.g., the α-toxin of C. perfringens, an enzyme which is known to be a lecithinase.

There is a connotation to the word toxin itself, however, which should not be ignored. Clostridial α-toxin sounds much more impressive than calling the same protein Clostridial lecithinase. By calling a bacterial product a toxin, there is almost an implied guarantee that it is of relevance in the pathogenesis of disease. This is not necessarily the case, of course. Names based on observed effects in various laboratory test systems, whether in intact animals, isolated tissues or cell culture, or subcellular fractions may have the opposite effect. Staphylococcal α-toxin is a potent lysin for erythrocytes from certain species, notably the rabbit, but not for human erythrocytes (6). Hemolytic activity is a convenient way to assay for this toxin, but were it to be called α-hemolysin, many would tend to ignore it as a possible virulence factor in human staphylococcal disease. Perhaps demonstration of its effect on the skin, for which it is a potent necrotoxin, would revive interest in view of the clinical entity of the "scalded skin syndrome." However, it is another unrelated staphylococcal toxin called exfoliatin which is responsible for this particular staphylococcal syndrome (7). Until the relevant model can be investigated and Kochs postulates fulfilled, it is often difficult to establish the role of a toxin in the pathogenesis of a disease.

Shiga Bacillus Dysentery

A case in point is the disease caused by Shigella dysenteriae 1 which recently caused a major, explosive regional epidemic involving five countries in Central America, Mexico and the southwestern United States (8). The disease was characterized by the abrupt onset of diarrhea which evolved into the typical bloody, mucoid, purulent stool of dysentery in 24-48 hours, accompanied by abdominal pain, cramps, tenesmus and fever. In the early months of the epidemic, the case fatality rate was 8–15% in various rural villages in Guatemala and El Salvador, in part due to an interaction with the prevailing malnutrition. The organism responsible for this serious epidemic was a strain of classical S. dysenteriae 1 which had acquired resistance transfer factor and a multiple drug resistance episome. In biochemical characteristics the organism was identical to the original Shiga-Krüse bacillus (Table I), however the epidemic strain grew poorly on SS agar and was rarely isolated when this was the only selective medium used (9). As a consequence of this and because of the large number of amoeboid macrophages in the stool of patients, the diagnosis of amebiasis was often made. Since nearly one-third of the population were infected with E. histolytica, a prevailing regional public health problem, and occasional trophozoites were found early in the incubation period of Shiga dysentery, the diagnostic error was not without reason. It was the work of an astute microbiologist, Dr. Leonardo Jimenez Mata, that

TABLE I

Properties of Shiga-Krüse Bacillus

Property	Result
Motility	negative
TSI/KIA*	alkaline/acid
H_2S	negative
Catalase	negative
Indole	negative

Fermentation Reactions

Acid/No gas	Negative
glucose	mannitol
fructose	lactose
galactose	arabinose
raffinose	rhamnose
glycerol	xylose

* Triple sugar iron agar/Kligler iron agar.

established the true etiology of the epidemic (8). Mata isolated the organism using Tergitol-7 agar with triphenyl tetrazolium chloride (T7T), upon which it readily grew, and most importantly by going to the bedside to obtain rectal swabs which were directly streaked onto the agar. These extra efforts proved to be invaluable and were necessary, in fact, even though the organism was present in high concentration (10^7–10^9/gram) in the stools of patients. With the recognition of the true cause of the epidemic, its antibiotic resistance pattern (resistant to chloramphenicol, tetracycline, streptomycin and sulfonamides), and the cessation of inappropriate anti-amebic therapy, the case fatality rate dramatically declined. The importance of the classical microbiological work of Mata in this instance cannot, therefore, be overemphasized.

The isolate Mata had obtained behaved in the laboratory very much like virulent shigellae are supposed to. A drop of culture applied to the conjunctival sac of a guinea pig produced a purulent kerato-conjunctivitis due to invasion of the epithelium and induction of a marked inflammatory response (10). This characteristic invasiveness has been closely associated with virulence in this genus by the work of Samuel B. Formal, another outstanding microbiologist, and his colleagues working principally at the Walter Reed Army Institute of Research (11). When tested for its ability to invade intestinal epithelial cells in an animal study, the epidemic strain of Shiga bacillus was again positive (10). Dr. Formal was able to separate and grow a spontaneous mutant which produced an opaque rather than a translucent colony on nutrient agar. This variant organism behaved much like opaque mutants of other virulent shigellae studied by Formal's group, that is, it had lost the ability to invade cells (whether in the cornea or in the intestinal tract) and no longer was able to cause diarrhea or dysentery. Study of virulent S. flexneri 2a had previously indicated that both intestinal cell penetration and intracellular multiplication were necessary for disease to result (11). By mating the virulent shigella with a benign E. coli a hybrid resulted which retained the ability to penetrate the epithelium but could not flourish and multiply therein. As a result, the organism was rapidly cleared by the host defenses and again no disease resulted. The question remained unanswered, however, of what was actually happening in that intracellular milieu as a result of invasion and multiplication of the organisms to lead to clinical illness.

One possible biochemical mechanism to be considered was the production of a protein toxin active on the intestinal epithelial cell, that is to say an enterotoxin. The epidemic species was, in fact, already known to elaborate a protein toxin. As early as 1903 culture filtrates of S. dysenteriae 1 were demonstrated to produce paralysis and death upon parenteral injection into animals, which led to the designation of the active material as neurotoxin (12). Large doses of the filtrate or lysate of Shiga cultures given intravenously or intraperitoneally also were capable of causing hemorrhagic necrosis of rabbit intestine, particularly the cecum (13). Early workers thus often spoke of the presence of two toxins, neurotoxin and an enterotoxin. Some clarification was obtained by the 1920's when Olitsky and Kligler separated these two "toxic" activities into an antigenic protein toxin producing neurological manifestations, and classical lipopolysaccharide which was the cause of the intestinal manifestations (14). Thus was established the germ of a concept of endo-enterotoxin in the pathogenesis of Shiga bacillus dysentery. Once in the literature, such concepts have a long "shelf-life," and recent microbiology texts have continued to give prominent mention of the two-toxin hypothesis.

However, there was nothing really unique about the response to intravenous S. dysenteriae 1 lipopolysaccharide. LPS from nonpathogenic organisms could produce the same symptoms and signs, and thus it was difficult to give much credence to its role in the pathogenesis of Shiga dysentery. Nor did it seem likely that neurotoxin was of much importance in the disease either. The relevance of the neurological syndrome caused by neurotoxin to diarrhea and dysentery was not obvious. Even the concept that this molecule might be responsible for seizures during disease was untenable in view of their equal prevalence in other forms of shigellosis due to species not known to produce any protein toxin. Neurotoxin was thus relegated to the role of a toxin in search of a disease and the molecular pathology of bacillary dysentery remained unclear.

In the decade preceding the Central American epidemic of Shiga dysentery a most important model for the study of enterotoxins, first used at the end of the last century, was reintroduced and developed in the successful studies leading to discovery, isolation and purification of cholera toxin (15). In this model, segments of rabbit ileum are formed in situ by placing silk ligatures around the bowel every 7-10 cm. Material to be tested is injected transmurally into the intestinal lumen, following which the entire intestine with its intact blood supply is returned to the peritoneal cavity. After a number of hours isotonic fluid is secreted into the lumen in response to cholera toxin, whereas control loops remain dry as the gut continues to absorb fluid. The epidemic provided the stimulus to test in our laboratory cell-free preparations of S. dysenteriae 1 in this physiologically relevant model system. These studies showed that the epidemic strain did indeed produce an enterotoxin, a property which we soon verified for other pre-epidemic antibiotic-sensitive Shiga bacilli (16).

The next obvious question was the relationship of this newly discovered enterotoxin to the previously described neurotoxin. Neurotoxicity was therefore assayed by determination of lethality of parenterally injected toxin in mice. Tested in column fractions of enterotoxin, the two biologic activities eluted together in the same peak (16). At the same time Dr. W. E. van Heyningen who had prepared a large stock of neurotoxin in 1953 used for almost all subsequent studies of neurotoxin (a declining usage because of declining interest) kindly provided us with a supply of this preparation. Dr. van Heyningen's toxin proved to be biologically active after 20 years in the deep freeze, and to possess both neurotoxin and enterotoxin activities which behaved just like the newly made toxin (17). Further purification of toxin using isoelectric focusing (IEF) in a sucrose gradient column in our laboratory (17), and by IEF in polyacrylamide gels by Dr. George Grady and coworkers (18) has yielded a fraction isoelectric at pH 7.2, again with both neurotoxin and enterotoxin activities. From our present state of knowledge, therefore, it is likely that one protein possess both toxicities, depending on route of inoculation and animal model employed.

However both of these intact animal models have drawbacks. There is too much variation in results from day to day and animal to animal, the assays are time consuming and not terribly sensitive and animals are expensive to obtain and maintain. We therefore sought an easier, cheaper, more sensitive, more reproducible in vitro test for Shiga toxin. Earlier workers had demonstrated an effect of toxin on adherence to glass surfaces of cells in culture (19). When this property was reexamined, it seemed as though we had achieved our goals for an in vitro system. Cell detachment due to toxin was dose related, heat labile, specific for the protein toxin and not related to lipopolysaccharide, and neutralized by specific antibody (20). Using HeLa cells in monolayer culture, we demonstrated that toxin-related detachment of cells was the equivalent of cell death and could be miniaturized to reproducibly assay nanogram quantities of toxin. We termed this biologic property cytotoxicity, and proposed it as a model for the cytotoxic effects on intestinal epithelial cells caused by enterotoxin in the ligated rabbit ileal loop.

Neutralization by specific antibody indicated that we had an assay system which would allow assay for antibody in patient serum, as an indirect measure of toxin production in the intact host. Examination first of sera from patients naturally infected in the Central American epidemic demonstrated virtually 100% positivity for antibody during acute disease and for the first year afterwards (21). Subsequently, however, antibody disappeared, following a course similar to antibody against the polysaccharide somatic O antigens of the cell wall (22). An opportunity was provided to study serial pre- and post-exposure sera because of a continuing program for vaccine development using experimental human infections at the University of Maryland School of Medicine. These studies demonstrated that an IgM toxin-neutralizing antibody was produced in response to challenge with virulent wild type Shiga bacilli (22). A summary of knowledge at this point in our understanding would be that the organism elaborates a toxin in vitro, study of its properties in laboratory models suggests relevance to the human disease, and the specific toxin-neutralizing antibody response in patients indicates that it is produced during clinical illness in man.

However logical this is, these data do not constitute proof of the role of toxin in Shiga bacillus diarrhea or dysentery in man. It has become axiomatic in the study of infectious disease etiology to require fulfillment of a set of criteria known as Koch's postulates before acceptance of an organism as the causative one. These four criteria are: 1) the organism is always isolated from lesions; 2) it can be isolated in pure culture in the laboratory; 3) when inoculated into experimental animals it causes a similar disease; 4) the organism can then be recovered from lesions in these animals. Similar criteria can be proposed for the study of disease pathogenesis due to cell-free products of the causative microorganism; 1) all virulent strains of the particular organism produce the toxin; 2) the toxin can be specifically identified and purified in the laboratory; 3) when inoculated into experimental animals it causes a similar disease; and 4) specific blockade of its action prevents or reverses the signs and symptoms which it produces. Both sets of criteria, however, cannot always be satisfied. Some organisms cannot be cultivated in the laboratory, organisms may be toxigenic in the milieu of the host or a specific tissue but not in culture media in the laboratory, animal models are not always relevant and specific blockade may not be possible by pharmacologic means and antibody may not be effective for a variety of reasons. Thus failure to satisfy Kochs criteria or those outlined above for toxins does not rule out the etiologic relation of a microorganism or a cell-free product in the pathogenesis of disease.

Nevertheless, these principles are the guidelines for study of these questions, and answers can often be obtained by imaginative and thoughtful research. An example of this in the study of Shiga toxin is the work of Formal and colleagues (10). They set out to produce organisms with isolated virulence characteristics in order to study the requirement for invasiveness and/or toxigenicity. The four possible arrangements are shown in Table II. It was relatively simple to pick colonial mutants with altered invasiveness but which retained the ability to produce toxin in vitro. A more difficult task was to find

TABLE II

Virulence Features of S. dysenteriae Strains and in Vivo Correlates

Strain	Properties[1]		Reaction in man	
	Invasiveness	In vitro[1] toxigenicity	Disease production	Serum[2] antibody
Wild Type	Yes	Yes	Yes	Yes
Opaque Mutant	No	Yes	No	No
Chlorate-Resistant Mutant	Yes	No	Yes	Yes
Avirulent	No	No	?	?

[1] See reference 10.

[2] See reference 22.

a non-toxigenic but invasive strain. This was finally achieved through chemical mutagenesis using chlorate to select resistant organisms. When studied in animal model systems the invasive organisms were virulent irrespective of their ability to produce toxin. Thus it was reasonable to conclude that invasion and not toxin was the key to disease pathogenesis.

However, failure of an organism to produce a toxin in vitro may be simply because its requirements are not being met in the artificial laboratory system. The true test is in the experimental animal or in man himself. This could be approached using the antibody response as an indicator of toxin production in vivo. When studied by anti-cytotoxin neutralizing antibody assay, sera from subjects experimentally infected with the invasive "non-toxigenic" strain were found to contain IgM neutralizing antibody like sera from subjects infected with the wild-type organism (22). The conclusion from these studies is that the chlorate-resistant mutant does not elaborate toxin in vitro under the conditions studied but does produce the same antigenic protein in the milieu of the intact host. The assumption implicit in this, though unproven, is that the antigen elaborated in vivo represents biologically active toxin itself.

The identification of a second cytotoxic product of the Shiga bacillus formed in vitro, physically distinct (size, isoelectric point) from the entero/neurotoxin and sharing only the cytotoxicity property of the larger toxic moiety has served to emphasize the lack of proof for this assumption (17, 18). Anti-cytotoxin antibody may not be directed towards the entero/neurotoxin at all, but rather a separate new toxin active in vitro against HeLa cells with unknown relevance vis-à-vis disease. Our research is now directed towards dissecting the questions implicit in these findings so that reasonable conclusions can be reached.

This may be the most important area for investigation of these questions. For in looking ahead to future attempts to satisfy criterion (4) above, I can foresee difficulties in trying to obtain valid data. Our current studies indicate that toxin must be transported into the cell for biologic activity (cytotoxicity in HeLa cells) to be expressed. If we assume for discussion that the enterotoxin must also reach an intracellular site as well then neutralizing antibody may not be capable of acting once toxin is within the cell. Antibody against cholera toxin has been shown to prevent binding of toxin to the surface GM_1 ganglioside receptor, an event that occurs outside the cell (23). However, an essential part of shigella virulence is the property of invasiveness. Viewed in the perspective of the toxin hypothesis, intraepithelial cell penetration and multiplication can be seen as a mechanism to circumvent the uptake and transport of extracellular toxin and the effect of antibody. The intracellular milieu may be particularly appropriate for toxin production, and rather small quantities could be extremely effective, being delivered to its site of action by the efforts of the organism to gain entrance through the epithelial cell membrane. In addition to the challenge to investigate these questions, the implications for development of new therapeutic or public health methods to control the disease are unusually broad. The acceptance of these challenges is an acceptance to proceed with sound laboratory investigation, and to proceed beyond the boundaries of current dogma. There can be no better statement of the role of contemporary microbiology in the investigation of disease mechanisms, control and prevention.

References

1. *Dorlands Illustrated Medical Dictionary*, 24th Edition, W. B. Saunders Co., Philadelphia, 1965.
2. Banwell, J. G. and Sherr, H.: The Effect of Bacterial Enterotoxins on the Gastrointestinal Tract, Gastroenterology 65:467–497, 1973.
3. Bonventre, P. F., Lincoln, R. E., and Lamanna, C.: Status of Bacterial Toxins and Their Nomenclature: Need for Discipline and Clarity of Expression, Bact Rev 31:95–109, 1967.
4. Moreau, S. C. and Skarnes, R. C.: Host Resistance to Bacterial Endotoxemia: Mechanisms in Endotoxin Tolerant Animals, J Infect Dis 128:S122–S133, 1973.
5. Grady, G. F. and Keusch, G. T.: Pathogenesis of Bacterial Diarrheas, New Engl J Med 285:831–840, 891–900, 1971.
6. Arbuthnott, J. P.: Staphylococcal α-Toxin. In: *Microbial Toxins*. Edited by T. C. Montie, S. Kadis, and S. J. Ajl. Academic Press, New York 1970, p. 189–236.
7. Melish, M. E. and Glasgow, L. A.: Staphylococcal Scalded Skin Syndrome: The Expanded Clinical Syndrome, J Pediat 78:958–967, 1971.
8. Mata, L. J., Caceres, A., and Torres, M. F.: Epidemic Shiga Dysentery in Central America, Lancet 1:600–601, 1971.
9. Mata, L. J., Gangarosa, E. J., Caceres, A., Perera, D. R., and Mejicanos, M. L.: Epidemic Shiga Bacillus Dysentery in Central America. I. Etiologic Investigations in Guatemala, 1969, J Infect Dis 122:170–180, 1970.
10. Gemski, P., Jr., Takeuchi, A., Washington, O., and Formal, S. B.: Shigellosis due to Shigella dysenteriae l. Relative Importance of Mucosal Invasion versus Toxin Production in Pathogenesis, J Infect Dis 126:523–530, 1972.
11. Formal, S. B., LaBrec, E. H., and Schneider, H.: Pathogenesis of bacillary Dysentery in Laboratory Animals, Fed Proc 24:29–34, 1965.
12. Conradi, H.: Ueber lösliche durch aseptische autolyse erhaltene giftstoffe von Ruhr-Und Typhusbazillen, Dtsch Med Wchnschr 29:26–28, 1903.
13. Flexner, S. and Sweet, J. E.: The Pathogenesis of Experimental Colitis and the Relation of Colitis in Animal and Man, J Exp Med 8:514–535, 1906.
14. Olitsky, P. K. and Kligler, I. J.: Toxins and Antitoxins of Bacillus dysenteriae Shiga, J Exp Med 31:19–33, 1920.
15. De, S. N. and Chatteijee, D. N.: An Experimental Study of the Mechanism of Action of Vibrio cholerae on the Intestinal Mucous Membrane, J Pathol Bacteriol 66:559–562, 1953.
16. Keusch, G. T., Grady, G. F., Mata, L. J., and McIver, J.: The Pathogenesis of Shigella Diarrhea. I. Enterotoxin Production by Shigella dysenteriae I., J Clin Invest 51:1212–1218, 1972.
17. Keusch, G. T. and Jacewicz, M.: Pathogenesis of Shigella Diarrhea. V. Relationship of Shiga Enterotoxin, Neurotoxin and Cytotoxin, J Infect Dis 131:S33–S39, 1975.
18. McIver, J., Grady, G. F., and Keusch, G. T.: Production and Characterization of Exotoxin(s) of Shigella dysenteriae 1, J Infect Dis 131:559–566, 1975.
19. Vicari, G., Olitski, A. L., and Olitski, Z. The Action of the Thermolabile Toxin of Shigella Dysenteriae on Cells Cultivated in Vitro, Br J Exp Pathol 41:179–189, 1969.
20. Keusch, G. T., Jacewicz, M., and Hirschman, S. Z.: Quantitative Microassay in Cell Culture for Enterotoxin of Shigella dysenteriae 1, J Infect Dis 125:541, 1972.
21. Keusch, G. T. and Jacewicz, M.: Serum Enterotoxin-Neutralizing Antibody in Human Shigellosis, Nature (New Biology) 241:31–32, 1973.
22. Keusch, G. T., Jacewicz, M., Levine, M. M., Hornick, R. B., and Kochwa, S.: Pathogenesis of Shigella Diarrhea. Serum Anti-Cytotoxin Antibody Response produced by Toxigenic and "Non-Toxigenic" S. Dysenteriae 1, J Clin Invest 57:194–202, 1976.
23. Walker, W. A., Field, M., and Isselbacher, K. J.: Specific Binding of Cholera Toxin to Isolated Intestinal Microvillous Membrane, Proc Nat Acad Sci 71:320–324, 1974.

The Mount Sinai Journal of Medicine
Vol. 44, No. 1, January-February, 1977
Printed in U.S.A.

Listeria monocytogenes: Another Look at the "Cinderella among Pathogenic Bacteria"

EDWARD J. BOTTONE, Ph.D. and MARCELINO F. SIERRA, Ph.D.

Introduction

The first description of Listeria monocytogenes is attributed to Murray, Webb, and Swann (1) who, working in England in 1926, recovered the bacterium from the livers of sick rabbits and guinea pigs during epizootic septicemic disease. Because these animals showed an increase of circulating monocytes, these authors named this heretofore unidentified microorganism Bacterium monocytogenes.

The following year, Pirie recovered a similar microorganism from the livers of African gerbils in which he noted areas of focal necrosis (2). As published descriptions of this microorganism were not definitive, Pirie proposed the name Listerella hepatolytica: the binomial being arrived at in honor of Pirie's chief, Sir Spencer Lister, as well as the observed liver pathology. Subsequently, the English and African isolates were shown to be identical and the name Listerella monocytogenes was proposed, but as the genus name had already found usage in biology, Pirie in 1940 suggested the present designation Listeria monocytogenes (3) which was subsequently adopted in the 6th edition of *Bergey's Manual of Determinative Bacteriology.*

The first well-documented isolation of L. monocytogenes was reported in Denmark by Nyfeldt in 1929 (4) who recovered the bacterium from the blood of patients with an infectious mononucleosis-like disease. Although Nyfeldt considered L. monocytogenes as the etiologic agent of mononucleosis, little evidence for this relationship has been forthcoming and it has subsequently been shown that monocytosis is not a usual manifestation of listeriosis (5). Numerous reports have appeared from all over the world documenting the association of Listeria with a wide variety of infections predominantly in animals and sporadically in man. Gradually, an increasing awareness of listeric infections in man became apparent first in Europe and then in North America culminating in 1957 when Seeliger and Cherry published their monograph dealing with human infections caused by Listeria monocytogenes (6).

Among the reports that appeared between 1951 and 1958 were several incriminating Listeria as the cause of repeated abortions and perinatal infections (7, 8, 9). In 1959, Rabinowitz (10) and in 1960, Rappaport (11) and their respective coworkers advanced this relationship with their reports noting

From the Department of Microbiology, The Mount Sinai Hospital, New York, N. Y. 10029, and the Department of Pathology, Downstate Medical Center, Brooklyn, N. Y. 11203.

Requests for reprints should be sent to: Dr. Edward J. Bottone, Department of Microbiology, The Mount Sinai Hospital, Fifth Avenue and 100 Street, New York, N. Y. 10029.

the isolation of Listeria from the genital tract of women and suggested a role for this microorganism as a significant pathogen in the newborn period as well as causing habitual abortion. L. monocytogenes infections in man also may result in meningitis, conjunctivitis, septicemia, endocarditis, and osteomyelitis (6, 12). Recently, Listeria infections have been recognized with increasing frequency in patients with severe underlying diseases particularly those affecting the immune system (13, 14).

The present report is based upon our experiences at The Mount Sinai Hospital and Downstate Medical Center with 37 cases of infection due to L. monocytogenes, ten of which have been previously described by Buchner and Schneierson (15). Included herein is a review of the literature relative to the laboratory and clinical aspects of infections caused by Listeria monocytogenes.

Taxonomy and Nomenclature

The 7th edition of Bergey's Manual (1957), listed the genus Listeria in the family Corynebacteriaceae, which contained only one species, Listeria monocytogenes. However, the recently published (1974) 8th edition (16) places the genus Listeria with the family Lactobacillaceae under the heading *Genera of Uncertain Affiliation.* Four species are included: L. monocytogenes, L. denitrificans, L. grayi, and L. murrayi. As these latter species have only been isolated a few times from animal sources and never from humans, the validity of listing these species within the genus Listeria is questioned by both the authors of the Manual, as well as by those describing these new species (17). It would therefore appear that the genus Listeria contains only one species, L. monocytogenes, and that other organisms presumed to be separate species are either of another genus altogether (16, 17) or are biochemical variants of L. monocytogenes (18).

Morphology

Morphologically, L. monocytogenes is poly-diverse. The milieu in which it is growing appears to markedly influence its morphology. When observed directly in smears of a purulent exudate, gram-positive, non-spore-forming cocci, diplococci, and diplobacillary forms may be observed along with typical bacilli (Fig. 1). The cells may also be found singly, in short chains, and in diphtheroid-like arrangements consisting of X and V forms and palisade formation. Marked pleomorphism is seen in smears prepared after 18–24 hours growth in artificial media. In broth cultures, long bacillary forms are frequently observed whereas on solid media, coccobacillary and short rods measuring 1.2 × 0.5 μ arranged singly or in palisades predominate (Fig. 2). Gram variability may be observed after growth in artificial media for periods longer than 24 hours. In smears prepared from such media, it is not uncommon to find Gram-negative cells displaying all of the morphological entities noted above. Because of this diversity in morphology and staining characteristics, L. monocytogenes is often mistaken for a Corynebacterium spp., Streptococcus

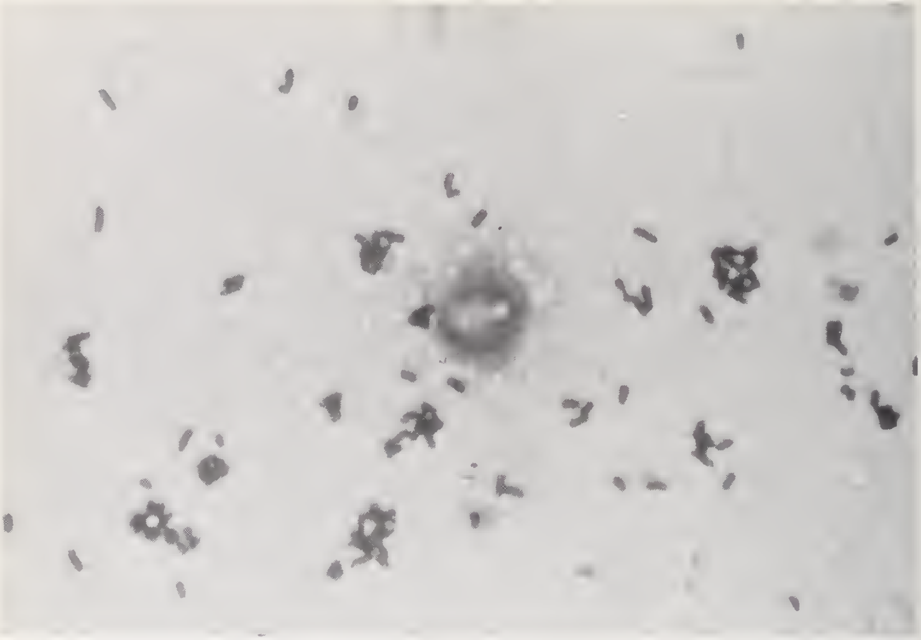

FIG. 1. Smear of peritoneal exudate showing pleomorphic cells of Listeria ranging from coccal, diplococcal, and bacillary forms (× 1000).

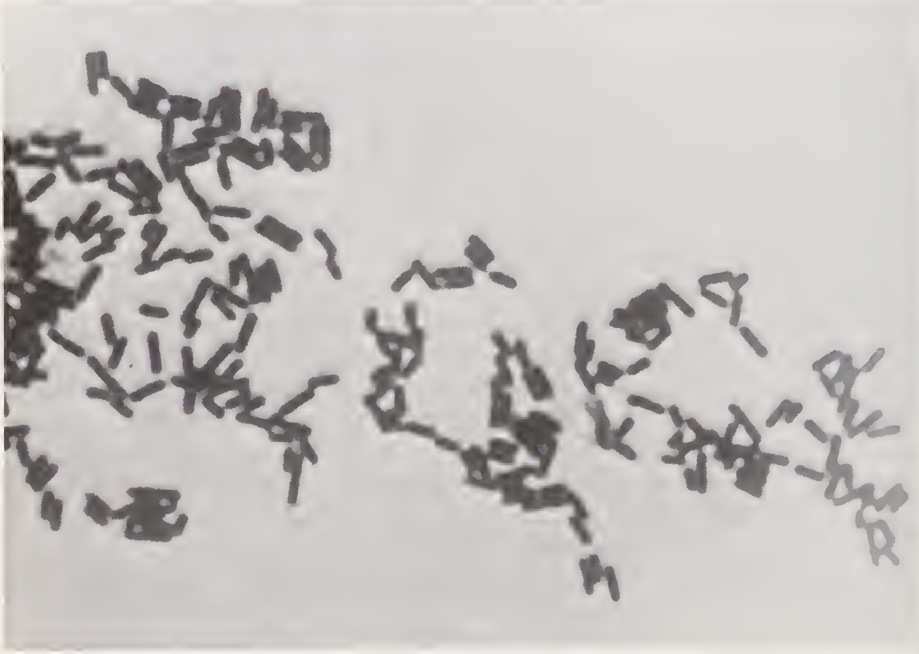

FIG. 2. Smear of 18-hour broth culture showing predominance of bacillary forms arranged singly, in short chains, and palisade formation (× 1200).

spp. (especially enterococci), Bacillus spp., Haemophilus spp. and even occasionally, as an Enterobacteriaceae.

The presence of capsular-like material has been reported in cultures of L. monocytogenes incubated at 3.0° to 5°C, but not at 37°C (19). Smith and Metzger (20), utilizing electron microscopy, have demonstrated a capsule which was only synthesized when the organism was grown in trypticase soy medium enriched with serum and glucose.

There is extensive discussion in the literature regarding the difficulty of isolating L. monocytogenes from clinical material. It is often suggested that specimens should be kept at low temperatures for prolonged periods of time before isolation is attempted (12, 18). This procedure, however, is contrary to the urgent requirements for bacteriological examination in the clinical circumstance, and it has been our experience as well as that of others (15), that in cases of meningitis and septicemia the organism is readily recoverable within 24 hours in a variety of routinely available media. This fact is particularly noteworthy as Gram-stained smears of purulent cerebrospinal fluid often fail to reveal the presence of Listeria (23), yet this organism is recovered in the absence of "cold-enrichment."

With regard to motility, when grown in a liquid medium at 35–37°C, L. monocytogenes is non-motile or, at best, only sluggishly motile whereas at 22–25°C, it exhibits a highly active, characteristic, tumbling, pinwheel type of motility. If a tube of semi-solid agar is stabbed and incubated at 25°C, a distinctive "umbrella" pattern of motility is observed radiating from the line of inoculation.

Cultural Characteristics

L. monocytogenes is a facultative organism which grows readily at a neutral to slightly alkaline pH on most routinely used bacteriological medial. Listeria grows within a temperature range of from 4°C to about 45°C reaching an optimal growth rate at 35–37°C. On sheep blood agar after 24 h incubation at 37°C, the colonies are round, slightly raised with a smooth surface and exhibit a narrow zone of diffuse hemolysis in contrast to that observed with the Group B streptococcus with which it may be confused (Fig. 3). This hemolysis is distinctive in that the hemolyzed area is not clear but rather hazy and has been described as a "ground-glass type" of hemolysis (15). L. monocytogenes has also been reported to be hemolytic on horse, rabbit, human and ox blood (21). When the organism is grown on a colorless medium and viewed with a dissecting microscope with the aid of obliquely transmitted light, the colonies display a distinctive blue-green color (22).

Biochemical Characteristics

The biochemical characteristics including the fermentation pattern of Listeria have been extensively investigated (12, 18, 21). Although L. monocytogenes is poly-diverse with regard to morphology and Gram-stain reaction, it

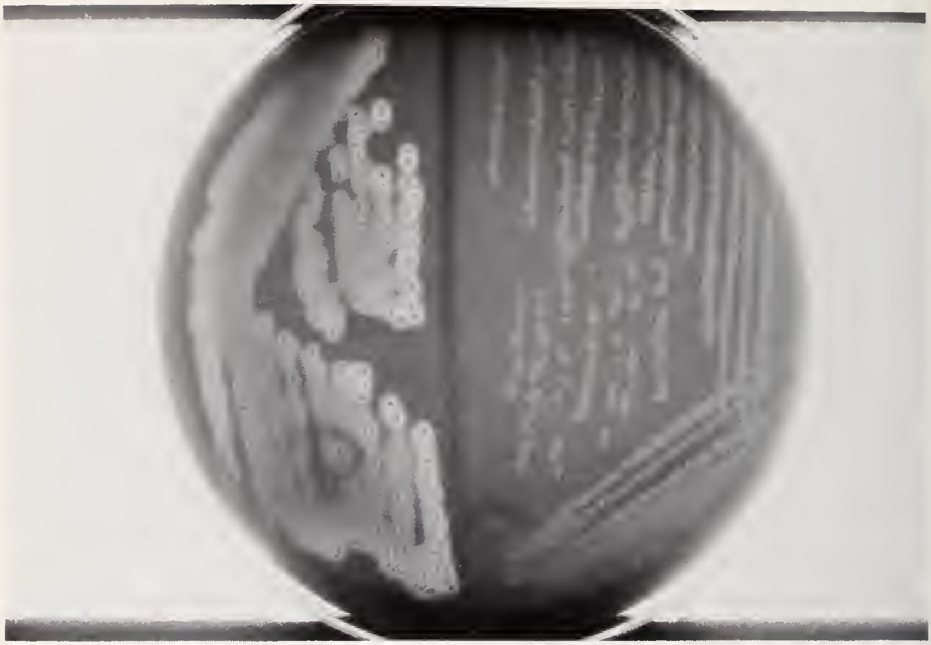

Fig. 3. Twenty-four hour sheep blood culture contrasting "ground glass" beta hemolysis of Listeria (right) with that of the group B streptoccoccus, S. agalactiae (left).

is biochemically uniform. Among the salient features of this species that easily aid its identification are positive catalase, methyl-red (MR), and Voges-Proskauer (VP) tests, growth in the presence of 6.5% NaCl, and 10 and 40% bile, hydrolysis of esculin, and fermentation of glucose, trehalose, cellobiose, and salicin within 24 hours. It is uniformly nitrate negative and does not deaminate phenylalanine, split urea nor hydrolyze starch (Table I). Although each of the above tests is a routine procedure in most diagnostic laboratories, we refer the readers to the finely detailed paper of Wetzler et al (21) for a description of the methods for the tests described.

Differentiation from Morphologically Similar Species

The differentiation of L. monocytogenes from other microorganisms such as Corynebacterium spp. and Streptococcus spp. (particularly Group D) is often thought to be a difficult task. It is our experience, however, that the organism is relatively easy to identify if particular attention is paid to patient history, source of specimens, morphology, hemolysis on 5% sheep blood agar, catalase production, and characteristic "tumbling" motility at 25°C (Table II). In addition, if mice, rabbits or guinea pigs are available, the instillation of a saline suspension of the L. monocytogenes into the conjunctival sac of the animals will cause a rapid and purulent conjunctivitis (Fig. 4) as described by Anton (24). In spite of the purulent exudate resulting from such conjunctival instillation of Listeria, the inoculated organism cannot be recovered from cultures of conjunctival swabs of the involved eye. This fact may be attributed to the rapid penetration of, or phagocytosis by, epithelial cells of the conjunctiva. Zimianski, Dawson, and Togni (25) have shown that epithelial cell penetration by Listeria occurs as early as 15 min following conjunctival instillation. The initial event appears to be adherence of the organism to the exposed epithelial surfaces followed by uptake well in advance of a noticeable polymorphonuclear response. Indeed, within two hours of inoculation, these investigators could show that Listeria were found almost exlusively within

TABLE I

Diagnostic Characteristics of Listeria monocytogenes

Motility: 22°C	Positive ("tumbling")
37°C	Negative
Action on 5% sheep blood agar	Beta hemolysis
Catalase	Positive
Methyl red	Positive
Voges-Proskauer	Positive
6.5% NaCl tolerance	Positive
10, 40% bile tolerance	Positive
Esculin hydrolysis	Positive
Nitrate reduction	Negative
Phenylalanine deaminase	Negative
Urease production	Negative
Starch hydrolysis	Negative
Fermentation:	
Glucose	Positive
Trehalose	Positive
Cellobiose	Positive
Salicin	Positive

TABLE II

Differentiation of Listeria from Morphologically Similar Microorganisms

Species	Morphology	Motility 22°C	Catalase	Hemolysis	Salicin	Trehalose
L. monocytogenes	Pleomorphic, cocci, rods, filaments	+	+	Beta	+	+
Erysipelothrix insidiosa	Pleomorphic, slender rods	0	0	W (0)	0	0
Lactobacillus spp.	Pleomorphic rods	0	0	Alpha	V	V
Corynebacterium spp.	Pleomorphic rods	0	V	Beta (neg.)	0	V
Kurthia spp.	Pleomorphic, filamentous	+	+	0	0	0
Streptococci	Cocci	0	0	V	+	V

+ = Positive.
0 = Negative.
V = Variable.
W = Weak.

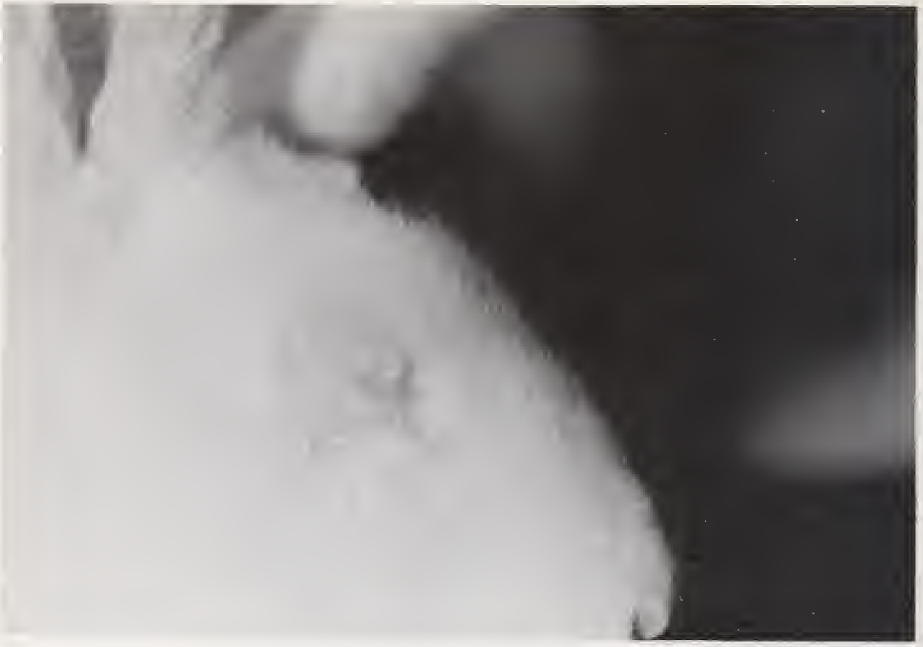

FIG. 4. Purulent conjunctivitis resulting from instillation of a Listeria into rabbit conjunctiva.

epithelial cells, while a few appeared within polymorphonuclear leukocytes which were just beginning to accumulate in the subepithelial and epithelial tissues. Capacity to penetrate corneal, conjunctival, urinary bladder, and small intestine epithelial cells, as the first stage in the pathogenesis of Listeria infections has been well documented by Racz and coworkers (26, 27) who ascribed to this occurrence the term "epithelial cell phase of intracellular parasitism." In our own studies (28), we have demonstrated that Listeria also penetrate Hela cells in tissue culture (Fig. 5).

Serology

The most definitive early serological studies of L. monocytogenes were performed by Patterson (29) in 1940 who examined the somatic (0) and flagellar (H) antigens of this microorganism and recognized four distinct serologic types, namely types 1, 2, 3, and 4. Subsequent studies have resulted in the assignment of three additional serotypes and 11 subtypes within the major serotypes (6). The most frequently identified serotypes from human sources are types 1 and 4 (12). Of nine strains from the present series submitted to the Center for Disease Control for serological typing, three each were designated types 1a, 4b, and 4d. Serotype 5, described by Ivanov (30) and characterized by Cooper and Colleague (31), is distinguished from more typical L. monocytogenes strains examined mainly by producing large zones of double hemolysis on ovine blood agar, and by its somewhat restricted fermentative capability.

Serologic diagnosis of listeriosis has been attempted by assaying patients' sera for antibody titers by utilizing precipitation, complement fixation, and hemagglutination tests (12). Results, however, have been confusing and not reproducible. These difficulties have been attributed to the presence of the Rantz antigen which is commonly found among Gram-positive microorganisms as well as to other cross-reacting antigens distinct from the Rantz antigen (32).

Spectrum of Listeric Infections

Listeria monocytogenes, referred to as a "Cinderella among the pathogenic bacteria" by Gray and Killinger (12) because of its long lack of recognition as a human pathogen, still retains many of the nuances of a fairy tale heroine. Striking hard in the animal kingdon, it is a cause of abortion, perinatal infection, septicemia, and meningoencephalitis, without regard to species or state of well-being of the host. This microorganism which, since Gray and Killinger's monograph appeared in 1966, has found its "golden slipper" manifests itself in man 1) predominantly at the extremes of life, i.e., the very young or the elderly, 2) in normal, healthy persons, and 3) in hosts with compromised immune status because of disease and/or drugs.

In the analysis of any large series of listeric infections (33, 34), the above distribution is usually observed with perhaps one new proviso, that is an increasing incidence of bacteremia and meningitis in patients with

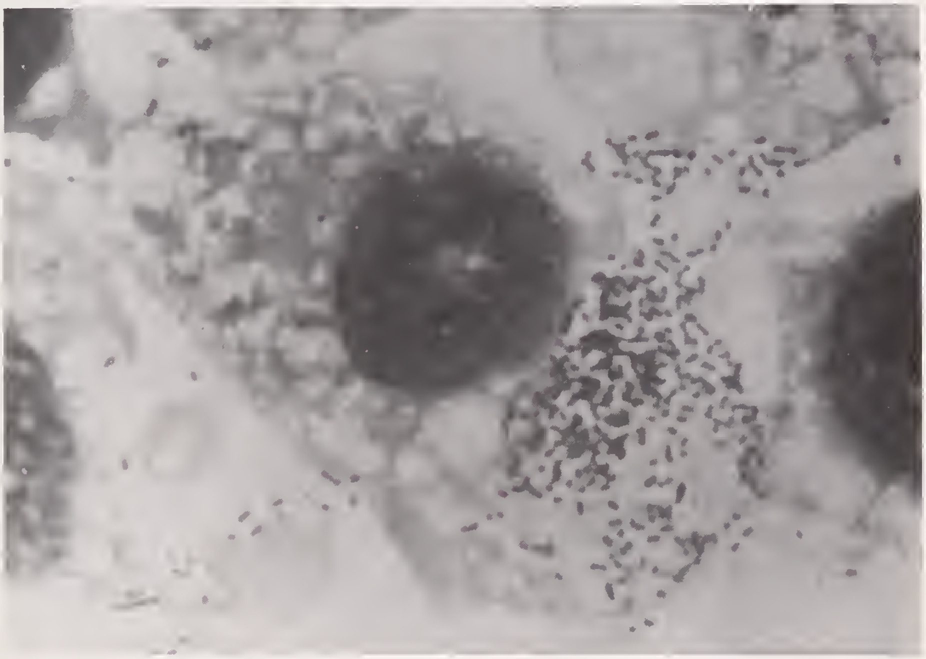

FIG. 5. Penetration of HeLa cells by Listeria. Note presence of numerous organisms within cytoplasm of large epithelial cell.

immunosuppressive underlying disorders (14, 15). As shown in Table III, the present series confirms many of these general features of the manifestations of listeric infections. Thirty-two of the 44 isolates recovered from the 37 patients were recovered from a blood culture, 8 from cerebrospinal fluid, and 1 each from cervix, leg abscess, hepatic abscess, and placenta.

Of the 32 patients showing Listeria septicemia, five had concomitant meningitis which yielded Listeria on culture of the cerebrospinal fluid, and two patients showed Listeria from another site: a leg abscess in a renal transplant subject, and placenta and hepatic abscess in a newborn. Of this group of 32 patients, 6 were recipients of renal transplants while 16 patients had various forms of malignancies. Two patients, one renal transplant recipient, and one patient with Hodgkins's disease had an antecedent history of cryptococcal meningitis.

Although the association of listeriosis with neoplastic and lymphproliferative diseases is well documented (13, 14, 15), infection caused by this species in organ transplant patients is an emerging complication. Prior to the present series in which 6 renal transplant recipients developed listeriosis, a single case is listed among the 12 diagnosed by Medoff, Kunz, and Weinberg in 1971 (33) and organ transplantation is mentioned by Busch (34) but not emphasized as a contributing factor in his review of listeric infections in the United States from 1967–1969. Listeria sepsis was not reported by Rifkind (35), Burgos-Calderon (36), McDonald (37), and Smoler (38) and their respective coworkers in a total of 136 patients with infections following renal transplantation. Factors thought to contribute to the high incidence of infections in these patients are related to high-dose immunosuppressive therapy during rejection crises which

TABLE III

Source of Isolates and Associated Condition of Patients Infected with Listeria monocytogenes

Associated Condition	No. Patients	Source				
		Blood	CSF	Abscess	Placenta	Cervix
Renal Transplant*	6	6	0	1 (leg)		
Lymphoma	7	7				
Leukemia						
Reticulum Cell*	1	1	1			
Lymphoblastic	1	1	1			
Chronic Lymphocytic	1		1			
Acute Myelogenous	1	1				
Solid Tumors	5	5				
Prematurity*	3	2		1 (hepatic)	1	
Pregnancy	1					1
Paraplegia*	2	2	1			
Vasculitis	1		1			
RHD, Alcoholism	1	1				
Ulcerative Colitis	1		1			
Anemia	1	1				
Unknown*	5	5	2			

* Listeria isolated from more than one site.

may result in agranulocytosis, defective cell-mediated and immune responses, steroid-induced diabetes, and hypogammaglobulinemia. In this regard, the advent of organ transplantation appears to have ushered in a new population of hosts susceptible not only to a variety of Gram-positive and Gram-negative microbial species of known pathogenicity, i.e., staphylococcus, enterobacteria, but also to opportunist pathogens such as Cryptococcus, Pneumocystis carinii, Mucoraceae (36, 39) and Listeria monocytogenes, to name but a few.

In most instances, the source of infection in renal transplant recipients is thought to be of an endogenous origin (35, 36, 37) particularly as a result of hematogenous "seeding" of areas of decreased local resistance by intestinal flora (37). As the intestinal tract has been proposed as the portal of entry of Listeria as well as the reservoir for this species in animals and humans (1, 40, 41, 42), it is reasonable to assume that Listeria sepsis in renal transplant recipients originates from the intestinal canal and is hence also of endogenous origin. Indeed, Racz and coworkers (27), using an experimental animal model, have definitively shown that Listeria are capable of penetrating the epithelial cells of the small intestine and multiplying within them (analogous to Salmonella and Shigella) in their initial phase of enteritis.

Bacteremia was the most prominent manifestation of listeric infection in the present series accounting for 90% of the isolates in contrast to previous reports (23, 33) in which meningitis was the most common symptom in both immunocompromised and normal hosts. Of the 37 patients discussed, 3 (chronic lymphocytic leukemia, vasculitis, ulcerative colitis) presented clinically with meningitis from whom Listeria was recovered from the cerebrospinal fluid. The remaining 5 spinal fluid isolates were recovered from patients in whom Listeria was also isolated from blood cultures. It appears particularly noteworthy that 18 patients with severe underlying disorders (renal transplant, lymphoproliferative disease, solid tumors) yielded L. monocytogenes only from blood cultures.

Granulomatous sepsis of the newborn, one of the more readily recognized listeric infections, is characterized by the presence of miliary granulomata in the liver, spleen, lungs, intestine and central nervous system (7, 43, 44). This perinatal disease may i) result in early abortion of the uterine contents, ii) be present at birth, or iii) develop within the first month of life. In the latter case septicemia or meningitis may predominate. The infection which is acquired mainly in utero or perhaps by passage through the birth canal, bears a striking similarity to perinatal infections caused by the group B streptococcus, S. agalactiae.

In the present series, severe in utero fetal infections were observed in three instances, two of which resulted in fetal wastage. In the first, a 27-year old gravida 9, para-3, admitted to the Downstate Medical Center because of fever and lack of fetal movement of two days duration, delivered a macerated fetus from which L. monocytogenes was recovered from cultures of blood and placenta. The second, a 27-year old gravida 8, para-3, with a history of two miscarriages, gave birth at The Mount Sinai Hospital to a child in fetal distress who expired within 9 hours. Antemortem blood cultures were sterile but L. monocytogenes was recovered from an umbilical culture. Postmortem examination revealed multiple granulomata in the liver and microabscesses in the esophagus and lung. L. monocytogenes was recovered from the hepatic abscesses and could be observed in Gram-stained smears of the histologic section as well (Fig. 6). Because of marked cyanosis unresponsive to oxygen therapy, the third patient, a premature infant, was transferred to The Mount Sinai Hospital where blood cultures yielded L. monocytogenes. This child recovered following penicillin and tetracycline therapy.

To account for such devastating in utero infections as noted above, Reiss and coworkers (7) postulated that the initiating event is maternal bacteremia followed by passage of the organism through the placenta into the fetal circulation with subsequent hematogenous dissemination to all organs. Aspiration of infected amniotic fluid may account for respiratory and gastrointestinal lesions.

In 1968–1969, the greatest number of cases (17%) reported to the Center for Disease Control occurred in infants less than four weeks old (34). However, in the present series, perinatal infection developing after birth was an infrequent occurrence, particularly at The Mount Sinai Hospital. This fact may well be attributed to the institutional practice of administering in the delivery room 50,000 units of penicillin G intramuscularly for the prophylaxis of neonatal gonococcal ophthalmia, a procedure which has also resulted in a marked reduction in the incidence of perinatal group B streptococcal disease (46).

Listeria meningitis is reportedly the most frequent manifestation of

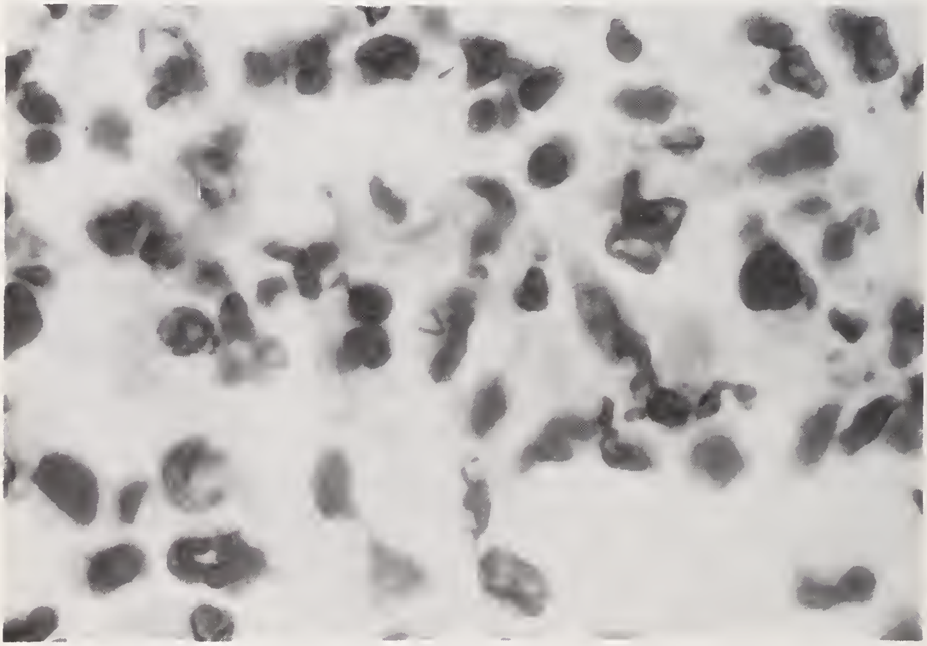

Fig. 6. Granulomatous hepatic abscess showing presence of "V" forms of Listeria in center of exudate.

perinatal disease (17). However, our data as well as those of other investigators (48) suggest a changing pattern. Although all three newborns in the present study had severe perinatal disease, two of whom presented within classic "granulomatosis infantiseptica" (7), none had meningitis. Listeria was recovered from the blood alone of two infants, and hepatic abscesses of the third.

To date, no satisfactory conclusion can been drawn as to whether or not postpartum listeriosis is contracted during delivery as a result of fetal passage through a colonized birth canal or is acquired in utero. In those instances where a premature infant is delivered macerated or in acute distress with granulomatosis infantiseptica, there is little doubt as to an in utero route of infection. In infants, however, who develop postpartum Listeria infection after three days, the evidence is less clear cut for incriminating the birth canal as the source of infection. For instance, although several investigators have been able to recover L. monocytogenes from vaginal and cervical cultures of mothers delivering infants who developed listeriosis following birth (3, 4, 41, 43, 49), other case reports have appeared in the literature in which listeriosis has developed in infants while bacteriologic culture of the vagina and cervix at the time of birth or shortly thereafter failed to reveal the presence of Listeria (43). In addition, nursery outbreaks of listeriosis have taken place where person to person spread and/or newborn to newborn spread of L. monocytogenes may occur (50). This hypothesis is particularly attractive as *Listeria* has been demonstrated in the meconium of healthy newborn infants without any clinical manifestation (43). Such infants may indeed serve as a source for dissemination of organisms in the newborn nursery.

Definitive data regarding the causal role of Listeria in repeated abortions are still wanting. While Rappaport and associates (11) presented strong evidence for such association by isolating this microorganism from cervical secretions of 25 of 34 women with a history of repeated abortions. Ansbacher and colleagues (51) recovered Listeria only once from 72 patients with similar obstetrical histories. In this sole instance, the baby was unaffected. Further, Macnaughton (52), Rabau and David (53), and Lawler (54) could find no evidence of Listeria in a total of 708 patients with histories of repeated abortions or perinatal wastage. In the latter three studies, each of the investigators encountered microorganisms which superficially resembled L. monocytogenes upon primary isolation but were subsequently shown not to be this species. Perhaps the marked incidence noted by Rappaport and associates might also be attributed to the presence of Listeria-like microorganisms in some instances rather than true L. monocytogenes. A careful look at the data of Rappaport shows that he recovered microorganisms which he considered to be Listeria upon demonstration of "small round colonies" on an enriched agar base (lacking blood) which showed upon microscopic examination of smears "typical Gram-positive rods as described by Gray et al." "Some" of these strains were sent to Dr. H.P.R. Seeliger "and those that arrived alive were designated L. monocytogenes 4b." No other biochemical, cultural or animal pathogenicity studies were included in Rappaport's identification of his isolates.

As pointed out by Lawler and colleagues (54), the rather impressive data of Rappaport et al (11) could be attributed to a regional focus in Israel. However, Rabau and David (53), also working in Israel, were unable to isolate L. monocytogenes from 554 cases of abortions (74 habitually) or demonstrate its past presence by serological methods and concluded "that L. monocytogenes is unlikely to be a major factor in the causation of abortion in this area."

The occurrence of listeriosis in previously healthy individuals has received reinforcement by the report of Medoff, Kunz, and Weinberg (33). Six of the eleven cases of listeriosis described by these investigators occurred in patients who had no evidence of an underlying disorder. In our series of 37 patients; however, all 32 from whom a case history was available had some evidence of predisposing illness. These included, in addition to the aforementioned associated conditions, alcoholism, anemia, ulcerative colitis, vasculitis, rheumatic heart disease, and paraplegia (Table III). While no immediate explanation is apparent for these case distributions, it does not appear to be related to differences in patient population observed at Massachusetts General Hospital or at our institutions.

Antimicrobial susceptibility

As shown on Table IV, no consistent resistance was observed to any single antimicrobial agent. While some strain variation existed with regard to susceptibility to cephalothin, kanamycin, methicillin, penicillin, and streptomycin, uniform susceptibility was observed with ampicillin, chloramphenicol, clindamycin, lincomycin, erythromycin, gentamicin and vancomycin. Of interest is that 3 of 21 isolates were resistant to tetracycline.

TABLE IV

Antimicrobial Susceptibility of Listeria monocytogenes as Determined by the Two-Tube Broth Dilution Method (45)

Agent	Concentration µg/ml	Number			
		Tested	S	MR	R
Ampicillin	5, 10	20	20	0	0
Cephalothin	7.5, 15	17	9	7	1
Chloramphenicol	7.5, 15	21	21	0	0
Clindamycin-Lincomycin	2, 10	18	18	0	0
Erythromycin	1, 2	16	16	0	0
Gentamicin	5, 10	6	6	0	0
Kanamycin	10, 20	8	7	0	1
Methicillin	5, 10	12	9	2	1
Penicillin	1, 10 (units)	18	17	1	0
Streptomycin	10, 20	12	11	1	0
Tetracycline	2, 4	21	17	1	3
Vancomycin	5, 15	13	13	0	0

S = Sensitive.
MR = Moderately resistant.
R = Resistant.

Various investigators have suggested and utilized a number of antimicrobial agents for the treatment of Listeria infections. Among the agents that have been recommended are ampicillin (55), gentamicin (18), chloramphenicol (6), penicillin (33), and tetracycline (15). However, as treatment failures have occurred with each agent, Moellering and associates (56) noted that "there is no consensus among various authors as to which antibiotic regimen is most effective." Macnair, White and Graham (55) used intrathecal ampicillin for the efficacious treatment of Listeria meningitis and recommended its usage in infections caused by this microorganism. Lavetter et al. (23), in their review of 25 cases of Listeria meningitis, showed that ampicillin was as effective as benzyl penicillin G and because of its superior efficacy and minor side effects, also suggested its utilization in this particular disease. On the other hand, because of the successful treatment of eight of their patients with penicillin in high doses (24 million units/day) for two weeks, Medoff, Kunz, and Weinberg (33) recommended this antibiotic for the treatment of Listeria meningitis and sepsis.

In their study of antibiotic synergism against L. monocytogenes, Moellering and colleagues (56) showed that in therapeutic concentrations, penicillin and ampicillin exert only a bacteriostatic rather than bactericidal action on Listeria. Although both these agents have had successful application against Listeria, based on their data, these investigators recommended combined antibiotic therapy with penicillin or ampicillin in combination with an aminoglycoside such as streptomycin or gentamicin. The rationale advanced for such combined therapy was based upon occasional reports of therapeutic failures with penicillin or ampicillin and the fact that a considerable number of cases of listeriosis occurs in patients with altered host defenses.

Conclusion

Nearly 50 years since its first description from human sources, Listeria monocytogenes still remains one of the least understood microorganisms encountered in clinical microbiology. This species which is capable of traversing phylogenetic barriers as well as those of age and well-being, continues to evade microbiologists and epidemiologists alike in their efforts to elucidate its pathogenesis and natural habitat. Indeed, at this very writing, we are only beginning more fully to appreciate the saprophytic existence of this species as a resident of plants, animal, and soil environments (57) from which sources it may gain access to human hosts. In this regard, the role of human intestinal carriers of L. monocytogenes in the spread of listeric infections also remains unresolved. In part, the lack of recovery and hence recognition of this species as a member of human fecal flora may be attributed to the limiting doctrines of examining stool specimens only for "enteric pathogens," namely enteropathogenic Escherichia coli and Salmonella and Shigella species, to the almost total exclusion of other known pathogens such as Vibrio parahemolyticus, Yersinia enterocolitica, Aeromonas hydrophilia and perhaps even L. monocytogenes.

The fascination for the continued study of this microbial species lies in the diversity of clinical syndromes associated with its presence and their understanding. Whle certain entities such as "granulomatosis infantiseptica" are well documented, other aspects of Listeria infections are poorly understood. For instance, the predilection of Listeria for the central nervous system tissue of humans and animals, particularly in pregnant individuals, is striking but as yet unexplained. Indeed, while these gravida may only experience a "flu-like syndrome," the in utero neonatal infections are devastating (12).

L. monocytogenes is a facultative, intracellular parasite and virulence of this organism seems to be related to the successful establishment of such residence. Aside from this parameter, L. monocytogenes has not been shown to produce an exotoxin and little is known about the role of surface components (antigens), and extracellular products (hemolysin) in 1) survival of this species within phagocytes, or 2) as mediators of an immune response. Toward these endeavors, Wilder and Edberg (58), using an in vitro monolayer assay consisting of mouse peritoneal macrophages, showed that smooth (virulent) Listeria survive intracellularly whereas rough (avirulent) strains are rapidly killed, and Kingdom and Sword (59) have demonstrated that while the hemolysin is antigenic, it is not effective as a protective immunogen. Additionally, Kingdom and Sword (6) noted that the hemolysin may injure cardiac tissue.

As such reports continue to appear, some of the "mystique" surrounding this "Cinderella" will give way to a keener insight into this "capricious and consistently inconsistent" microorganism (12).

Addendum

At the time of submission of this manuscript, Etheredge and colleages (61) have reported upon a case of Listeria meningitis in a renal transplant recipient, and cite two additional case reports.

References

1. Murray, E. G. D., Webb, R. A., and Swann, M. B. R.: A Disease of Rabbits Characterized by Large Mononuclear Leukocytosis, Caused by a Hitherto Undescribed Bacillus Bacterium monocytogenes (n. sp.), J Path Bact 29:407–439, 1926.
2. Pirie, J. H. H.: A New Disease of Veld Rodents "Tiger River Disease," Pub S Afr Inst Med Res 3:163–186, 1927.
3. Pirie, J. H. H.: Listeria: Change of Name for a Genus of Bacteria, Nature 145:264, 1940.
4. Nyfeldt, A.: Etiologie de la mononucleose infecteuse, Compt Rend Soc Biol 101:590–591, 1929.
5. Girard, L. F., and Murray, E. G. D. Listeria monocytogenes as the Cause of Disease in Man and Animals and Its Relation to Infectious Mononucleosis from an Etiological and Immunological Aspect, Am J Med Sci 221:343–352, 1954.
6. Seeliger, H. P. R. and Cherry, W. B.: Human Listeriosis, Its Nature and Diagnosis. U. S. Dept. of Health, Education and Welfare, Center for Disease Control, Atlanta, Ga. 1957.
7. Reiss, H., Potel, J., and Krebs, A. Granulomatosis infantiseptica (eine Allgemeininfektion bei Neugeborenen und Säuglingen mit miliaren Granulomen), Zbl ges inn ed 6:451–457, 1951.
8. Johnston, W. H., Morton, S. A., Wong, M. H., and Roy, T. E.: Septicaemia of the Newborn due to Listeria monocytogenes, Can Med Assoc J 73:402–405, 1955.

9. Lutton, C.: A Case of Neonatal Death due to Listeriosis and a Review of the Problem, Am J Obst Gynec 75:759-761, 1958.
10. Rabinowitz, M., Toaff, R., and Krochik, N.: Genital Listeriosis as a Cause of Repeated Abortion (In Hebrew), Harefuah 57:276-278, 1959.
11. Rappaport, F., Rahinowitz, M., Toaff, R., and Krochik, N.: Genital Listeriosis as a Cause of Repeated Abortion, Lancet 1:1273-1275, 1960.
12. Gray, M. L. and Killinger, A. H. Listeria monocytogenes and Listeric Infections, Bact Rev 30:309-382, 1966.
13. Simpson, J. F., Leddy, J. P., and Hare, J. D. Listeriosis Complicating Lymphoma. Report of Four Cases and Interpretative Review of Pathogenetic Factors, Am J Med 43:39-49, 1967.
14. Louria, D. B., Hensle, T., Armstrong, D., Collins, H. S., Blevins, A., Krugman, D., and Buse, M.: Listeriosis Complicating Malignant Disease. A New Association, Ann Int Med 67:261-281, 1967.
15. Buchner, L. H. and Schneierson, S. S.: Clinical and Laboratory Aspects of Listeria monocytogenes Infections, Am J Med 45:904-921, 1968.
16. Buchanan, R. E. and Gibbons, N. E.: *Bergey's Manual of Determinative Bacteriology*, 8th ed. Williams and Wilkins, Baltimore, 1974.
17. Stuart, S. W. and Welsheimer, H. J. Intrageneric Relatedness of Listeria Pirie, Int J Syst Bact. 23:8-14, 1973.
18. Bojsen-Moller, J.: Human Listeriosis, *Diagnostic, Epidemiological, and Clinical Studies.* Costers Bogtrykkeri, Copenhagen, 1971.
19. Jaegers, R. D. and Meyers, D. M. *Listeria monocytogenes*, a Study of Two Strains Isolated from Human Listeriosis, Can J Microbiol 1:12-21, 1954.
20. Smith, C. W. and Metzger, J. F. Demonstration of a Capsular Structure on Listeria monocytogenes, Path Microbiol 25:499-506, 1962.
21. Wetzler, T. F., Freeman, N. R., French, M. L. V., Renkowski, L. A., Eveland, N. C., and Carver, O. J.: Biological Characterization of Listeria monocytogenes, Health Lab Sci 5:46-62, 1968.
22. Gray, M. L.: A Rapid Method for the Detection of Colonies of Listeria monocytogenes, 261. Bakt I Abt Orig 169:373-377, 1957.
23. Lavetter, A., Leedom, J. M., Mathies, A. W., Ivier, D., and Wehrle, P. F.: Meningitis due to Listeria monocytogenes. A Review of 25 Cases, N Engl Med 285:598-603, 1971.
24. Anton, W.: Kritisch-experimenteller Beitrag zur Biologie des Bakterium monocytogenes. Mit besonderer Berücksichtigung seiner Beziehung zur infektiösen Mononucleose des Menschen, Zentralbl Bakeriol Parasitenk Abt I Orig 131:89-103, 1934.
25. Zimianski, M. C., Dawson, C. R., and Togni, B.: Epithelial Cell Phagocytosis of Listeria monocytogenes in the Conjunctiva, Investig Ophthal 13:623-626, 1974.
26. Racz, P., Tenner, K., and Szivessy, K.: Electron Microscopic Studies in Experimental Keratoconjunctivitis Listeriosa. Acta Microbiol Acad Sci Hung 17:221-236, 1970.
27. Racz, P. Tenner, K., and Mero, E.: Experimental Listeria Enteritis. 1. An Electron Microscopic Study of the Epithelial Phase in Experimental Listeria Infection, Lab Investig 26:694-700, 1972.
28. Sierra, M. F.: A Study of the Behavior of Listeria monocytogenes in the Guinea Pig Eye and in Tissue Culture. Master's thesis, Wagner College, 1970.
29. Patterson, J. S.: The Antigenic Structure of Organisms of the Genus Listerella, J Path Bact 51:427-436, 1940.
30. Ivanov, I.: La listeriose chez les ovins et les coprins, Bull Off Internat Epizool 48:571-573, 1957.
31. Cooper, R. F., Denis, S. M., and McMahin, K. J.: Characterization of Listeria Monocytogenes Serotype 5, Am J Vet Res 34:975-978, 1973.
32. Pease, P. E., Nicholls, L., and Stuart, M. R.: Evidence That Precipitin Cross-Reactions between Listeria, Erysipelothrix, and Bacillus licheniformis Are not due to the Rantz Antigen, J Gen Microbiol 73:567-569, 1972.

33. Medoff, L., Kunz, L. J., and Weinberg, A. N.: Listeriosis in Humans: An Evaluation, J Inf Dis 123:247–250, 1971.
34. Busch, L. A.: Human Listeriosis in the United States, 1967–1969. J Inf Dis 123:328–332, 1971.
35. Rifkind, D., Marchioro, T. L., Waddell, W. R., and Starzal, T. E.: Infectious Diseases Associated with Renal Homotransplantation, JAMA 189:397–401, 1964.
36. Burgos-Calderon, R., Pankey, G. A., and Figueroa, J. E.: Infection in Kidney Transplantation, Surgery 70:334–340, 1971.
37. McDonald, J. C., Ritchey, R. J., Fuselier, P. F., Lindsey, E. S., and McCracken, B. H.: Sepsis in Human Renal Transplantation, Surgery 69:189–193, 1971.
38. Smolen, J. K., Merrin, C. E., Surgalla, M. J., Moore, R. H., and Murphy, G. P.: Renal Transplant Recipients. Significance of Bacterial Infections, NY State J Med 74:2175–2181, 1974.
39. Hammer, G. S., Bottone, E. J., and Hirschman, S. Z.: Mucormycosis in Transplant Recipients: Case Report and Review of the Literature, Am J Clin Path 64:389–398, 1975.
40. Bojsen-Moller, J. and Jessen, O.: Occurrence of L. monocytogenes in Human Feces: Epidemiological and Pathogenetic Aspects, presented at the Third International Symposium on Listeriosis, 1966, Bilthoven, the Netherlands.
41. Bojsen-Moller, J. Human listeriosis. Epidemiological and Clinical Studies, Acta Pathol Microbiol Scand B 229 (Suppl):1, 1972.
42. Kampelmacher, E. H. and van Noorle Jansen, L. M.: Isolation of Listeria monocytogenes from Feces of Clinically Healthy Humans and Animals, Zentralbl Bakteriol (Orig) 211:353, 1969.
43. Ekelund, H., Laurell, G., Melander, S. Olding, L., and Vahlquist, B.: Listeria Infection in the Fetus and the Newborn, A Clinical, Pathological and Epidemiological Study, Acta Paediat 51:698–711, 1962.
44. Maguire, B. J. and Riley, H. D.: Infections due to Listeria monocytogenes in Infants and Children. Am J Med Sci 254:421–428, 1967.
45. Schneierson, S. S. and Amsterdam, D.: A Simplified Tube Procedure for the Routine Determination of Bacterial Sensitivity to Antibiotics, Am J Clin Path 31:81–86, 1959.
46. Steigman, A., Bottone, E. J., and Hanna, B. A.: Does Intramuscular Penicillin at Delivery Prevent Group B Beta Hemolytic Streptococcal Disease of the Newborn Infant? Letter to the editor, Pediatrics 87:496, 1975.
47. Hood, M.: Listeriosis as in Infection of Pregnancy Manifested in the Newborn, Pediat 27:390–396, 1961.
48. Variend, S. and Blumenthal, I.: Neonatal Listeriosis, Postgrad Med J 51:96–99, 1975.
49. Lutton, C.: A Case of Neonatal Death due to Listeriosis and a Review of the Problem, Am J Obst Gynec 75:759–761, 1958.
50. Florman, A. L. and Sundararajan, V.: Listeriosis among Nursery Mates, Pediat 41:784–788, 1968.
51. Ansbacher, R., Borchardt, K. A., Hannegan, M. W., and Boyson, W. A.: Clinical Investigation of Listeria monocytogenes as a Possible Cause of Human Fetal Wastage, Am J Obst Gynec 94:386–390, 1966.
52. Macnaughton, M. C.: Listeria monocytogenes in Abortion, Lancet 2:484, 1962
53. Rabau, E. and David, A.: Listeria monocytogenes in Abortion, Am J Obst Gynec Brit Comm 70:481–482, 1963.
54. Lawler, F. E., Wood, W. S., King, S., and Metzger, W.: Listeria monocytogenes as a Cause of Fetal Loss, Am J Obst Gynec 89:915–923, 1964.
55. Macnair, D. R., White, J. E., and Graham, J. M.: Ampicillin in the Treatment of Listeria monocytogenes Meningitis, Lancet 1:16–17, 1968.
56. Moellering, R. C., Medoff, G., Leech, I. Wennersten, C., and Kunz, L. J.: Antibiotic Synergism against Listeria monocytogenes, Antimicrobl Ag Chemother 1:30–34, 1972.
57. Weis, J. and Seeliger, H. P. R.: Incidence of Listeria monocytogenes in Nature, Appl Microbiol 30:29–32, 1975.
58. Wilder, M. S. and Edberg, J. C. Interaction of Virulent and Avirulent Listeria monocytogenes with Cultured Mouse Peritoneal Macrophages Inf and Immunity 7:409–415, 1973.

59. Kingdom, G. C. and Sword, C. P.: Biochemical and Immunological Effects of Listeria monocytogenes Hemolysin, Inf and Immunity 1:363-372, 1970.
60. Kingdom, G. C. and Sword, C. P. Cardiotoxic and Lethal Effects of Listeria monocytogenes Hemolysin, Inf Immunity 4:373-379, 1970.
61. Etheredge, E. E., Light, J. A., Perloff, L. J., and Spees, E. K.: Listeria monocytogenes Meningitis in a Transplant Recipient, JAMA 234:78-79, 1975.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 1, January-February, 1977
Printed in U.S.A.

Immunology of Bacterial and Fungal Infections

JACQUES M. SINGER, M.D.

The emergence of immunology as a modern science was a direct result of the investigations and successes achieved in bacteriology. With more recent advances, the sister sciences of immunology and microbiology, have become even more interrelated, so that in time, the two may merge to create a new discipline, i.e., "Immunomicrobiology." The ultimate goal of immunomicrobiology is to achieve a greater understanding of the intimate nature of cellular functions, through the application of immunologic techniques. In practical, clinical terms, advances in the field of immunology have influenced our approach to chemotherapy, transplantation, blood banking, neoplastic and autoimmune diseases and to the diagnosis and management of infectious diseases. With respect to the latter, though our understanding of the physiopathology of the cell remains at an elementary level, it may still prove meaningful, when treating a patient presenting an infectious disease, to consider his problem in terms of the related, underlying immunological phenomena and the possibility of reversing or improving his immunopathic condition.

Immunologic response to disease, or immunity, as it is defined today includes "all those physiological mechanisms which endow the animal with the capacity to recognize materials as foreign to itself, and to neutralize, eliminate, or metabolize them, with or without injury to its own tissue." Although two major levels of response are recognized, i.e., humoral and cellular, traditionally the emphasis was placed on humoral antibody research. Only recently has the importance of cell-mediated immunity been emphasized. The immune response is composed of both specific and nonspecific mechanisms. The natural (nonspecific) response may be cellular, where macrophages and polymorphonuclears play an important role or humoral, in which circulating mediators of the biological amplification system (complement, properdin, kinin, etc.) participate. The adaptive (specific) response, similarly includes cellular involvement via thymus-dependent T-cell lymphocytes, and humoral antibody production through stimulation by B-type (bursa, thymus-independent) lymphocytes. Each of these mechanisms will be discussed, in detail, in the text.

To date, most immunologic research directed at understanding the cellular, humoral and genetic response, employed nonliving antigenic material. There is no doubt that future investigations will attempt to study specific microbes,

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From the Department of Pathology, Division of Microbiology and Immunology, Montefiore Hospital and Medical Center, New York, N. Y. 10467.

Requests for reprints should be sent to: Jacques M. Singer, M.D., Montefiore Hospital & Medical Center, Department of Pathology, Division of Microbiology and Immunology, 111 East 210 Street, Bronx, New York 10467.

with regard to their chemical structures, genomes, antigenicity, metabolite toxin production and their adaptation to the host environment and to chemotherapy. Recently susceptibility to certain microbial diseases, such as leprosy, syphilis, candidiasis, brucellosis and coccidioidomycosis, has been traced to the presence of genetically linked histocompatibility antigens HL-A in the host.

Nonspecific Cellular Immunity

During a microbial invasion, the offending organisms first attach themselves to the mucosal surfaces of host tissue via complimentary chemical and conformational membrane sites (receptors). Responding to this challenge and thus acting as a primary defense mechanism, are the secretory immunoglobulins (IgE), which normally inhabit the secretions bathing the mucous membranes. These immunoglobulins limit microbial colonization by binding to bacterial surfaces, thus causing their agglutination and preventing their adherence to host tissue.

A cellular response (phagocyte mobilization) is also elicited early in the invasive process. Phagocytosis by polymorphonuclear (PMN) is a multifaceted response; it involves cellular recognition of foreign substances, and their ultimate ingestion and destruction. The presence of antibody, complement, and other enhancement factors, is an intrinsic part of the phagocytic process. This may be illustrated with virulent strains of pneumococci, and other encapsulated organisms, which do not readily adhere to phagocytes unless they are first coated with complement and specific antibodies (opsonization). The generation of peroxide and the release of bactericidal enzymes, subsequent to the ingestion process, are instrumental factors in causing the destruction of phagocytized parasites. A number of other substances and enzymes have recently been implicated in the neutrophilic breakdown of foreign matter. If the invader is successfully eliminated, the host response terminates at this stage.

Microbial penetration may elicit engulfment by histiocytes, as well as PMNs, thus triggering such inflammatory responses as complement activation, and coagulation and deposition of fibrin. These responses, along with phagocytosis, constitute the primary nonspecific responses of the host. Monitoring of the hosts responsiveness at this level may be accomplished via a number of laboratory determinations: WBC, count and differential, phagocytic index, bactericidal activity, quantitative nitro-blue tetrazolium (NBT), and quantitative measurement of specific leucocyte function. The enzyme deficiencies which may be measured include those for leucocyte NADH-oxidase, glucose-6-phosphate dehydrogenase (G-6-PD), glutathione peroxidase and leucocyte myeloperoxidase.

If bacteria are not successfully killed, they may continue to replicate locally, or they may invade regional lymph nodes, via the lymphatic channels. Within the lymph nodes, the invaders encounter the macrophages, which are additional elements of the phagocytic system. Macrophages bear surface receptors for aggregated IgG and for C3; they are able to bind antigen either by virtue of nonspecific sites or, through cytophilic antibodies bound to their IgG receptors. Via the receptors for IgG and C3, macrophages may also bind antigen-antibody (AgAb), and antigen-antibody-complement complexes.

It is believed that the macrophages initiate and are intimately associated with the immune response. The immediate contact of the bacterial antigens with T and B cells involves interaction with macrophages, or possibly other types of adherent lymphoid cells. During infection, the release of lymphokinins by T cells (e.g., migration inhibitor factor (MIF), aggregation factor (AF), chemotactic factor (CF), arming factor, and others, stimulates macrophages to increase their phagocytic and antibacterial activity (macrophage activation). The ubiquitous nature of macrophages is apparent if one considers the functions attributed to them: 1) the trapping of antigens; 2) the digestion of large molecules into smaller substances, more capable of initiating an immune response; 3) a role in the maintenance of lymphocyte function; 4) the coupling of antigen to RNA; and 5) the influencing of subsequent immune responses by lymphocytes via the transfer of informational RNA.

Certain intracellular parasites, namely Mycobacterium tuberculosis, M. leprae, Listeria, Brucella, Pasteurella, Salmonella, fungi, viruses, and some protozoa, are able to live and reproduce within the cytoplasm of macrophages. Their destruction is ultimately due to macrophage stimulated, cell-mediated responses.

Biological Amplification System—Nonspecific Humoral Immunity

In addition to the nonspecific cellular responses discussed, antigenic stimulation may cause the activation of one, or several enzyme systems of the blood, or of other kinds of cells. This humoral effector mechanism consists of complement–properdin and the kinin-forming, clotting, and plasmin systems. These represent amplification systems to humoral and cell-mediated immunity. Of these, complement is the only one which may be directly activated by either receptor cells, antigen, antibody, AgAb complexes, or by cell products. Complement is a protein composed of 9 fractions, (C1–C9). Activation of the 1st fraction sets into motion a "cascade effect," wherein each component induces the production of the one following it in the sequence. Complement can also be activated by an alternate pathway, in which activated properdin bypasses C1 and C2, acting instead directly on C3 production. This pathway can be stimulated by polysaccharide components of the cell wall, bacterial endotoxins, aggregated human IgA and yeast.

In patients with a gram negative bacteremia, there is a primary activation of the properdin-complement bypass, resulting in depressed levels of C3, C5, C6, C9 and properdin, while levels of C1, C2 and C4 remain normal. The decrease in C3 levels during a gram negative bacteremia with shock is of special significance since most other infections are accompanied by elevated C3 levels. This complement abnormality develops before the patient goes into shock. Monitoring of C3 levels by immunodiffusion techniques in patients with severe bacteremia has recently been advocated. Antibodies initiate the development of complement mediated lesion (C1–C9) producing holes in the membrane of the Gram-negative bacteria which allows access of serum lysosomes to the inner wall of the bacterium, which will result in cell death. Defects in the C3, C4, and C5 are associated with an inability to dispose of Gram-negative enteric bacilli and staphylococci.

As was mentioned, macrophages have specific binding sites for C3, allowing adherence of the antigen-antibody-C3 complex to the cell and thus facilitating phagocytosis. The bound C3 has a structural configuration different from that of the native molecule, and can provoke the formation of autoantibody immunoagglutinins. Cytolysis, inflammation triggered by immunoagglutination, and immunoadherence are a few of the biological roles of complement. Laboratory analysis of complement activity includes the determination of total complement levels and the measurement of C3 and C5 levels by immunodiffusion techniques.

The kinin-forming apparatus represents another humoral effector system. Kinins are a group of related polypeptides which have been enzymatically split from protein precursors (kininogens). Kinins are the most potent inducers of increased vascular permeability; they promote the sticking of leucocytes, and are mediators of acute inflammation.

The Hageman Factor (clotting factor XII) electrophoretically is a beta globulin of about 10,000 MN, which may be activated by AgAb complexes, collagen and basement membranes. Once activated, Hageman factor, and the fragments derived from it, are enzymatically active in the pathways involved in the inflammatory reaction, and are promoters of blood coagulation by their action on Factor XI (plasmin-thromboplastic antecedent). Activated Hageman factor can also convert plasminogen to plasmin, which in turn, activates the complement system. Thus Hageman Factor serves as a bridge, linking blood coagulation, fibrinolysis and the complement and kinin systems.

Though the nonspecific defense mechanisms described above are of vital importance, the development of specific, adaptive immune responses is indispensable for survival in normal individuals. When an antigen gains entrance into the lymph nodes or the blood it stimulates 1) T-lymphocytes which are responsible for cellular immunity and 2) B-lymphocytes which are involved in the synthesis of circulating antibodies (humoral antibody response).

1. *Cell mediated immunity*

The T-lymphocytes involved in this system are derived from thymus. They carry very little, or no immunoglobulins, and recognize proteins and carrier antigens. These cells are part of the memory cell system, have mitogenic susceptibility to pokeweed, and exhibit resistance to steroids and x-rays. T-cell reaction is mediated by the release of a group of substances known as lymphokinins. These lymphokinins have both direct and indirect effects on invasive bacterial cells. The most notable lymphokinins are the migration inhibitor factor (MIF), the blastogen-mitogen factor, the transfer factor, and interferon. The transfer factor is a small, non-antigenic, non-immunoglobulin, dialyzable polypeptide/polynucleotide or less than 10,000 MW, which converts both the normal host and its circulating lymphocytes to an antigen-specific responsive state. It has also been shown to transfer to normal recipients, delayed type, hypersensitivity (e.g., tuberculin, streptococcal protein, diphtheria toxoid, coccidiodin and skin homograft rejection reaction). Recently, transfer factor has been employed in the treatment of cellular immune deficiency caused by leprosy, mucocutaneous candidiasis, generalized vaccinia reactions, and certain types of cancer. Interferon, which, in in vitro and in vivo studies has been shown to block viral infection of host cells, is also used therapeutically. Many other lymphokinins have been detected, although not all of them have been characterized. These include skin reactive factor (SF), product of antigen recognition (PAR), lymphotoxin (LT), clonal inhibitor factor (CIF), proliferation inhibitor factor (PIF), inhibitors of DNA synthesis (IDS), lymph node permeability factor (LPF), as well as numerous others. An understanding of the actions of these mediators of cellular immunity and their relationship to macrophages and B cell functioning, would undoubtedly increase our ability to recognize, treat and conquer microbial invasions.

Infections that are controlled by cell-mediated immunity are those caused by both facultative intracellular parasites, including Mycobacteria, Salmonella, Pasteurella, Listeria, all fungi, and certain protozoa (Leishmania and Trypanosoma), and by obligate intracellular parasites such as viruses, rickettsiae, chlamydiae and protozoans such as Plasmodium, Toxoplasma and Pneumocytis.

Delayed hypersensitivity

While the immunological responses discussed represent beneficial defense mechanisms against infection, these same responses may prove harmful to the host. Thus continued antigenic stimulation may manifest itself as an immunologically-mediated disease phenomenon. An example is Type IV, delayed hypersensitivity, which involves the cell-mediated immune system and is thus mediated by sensitized T lymphocytes. Antigenically stimulated T cells elaborate lymphokinins, which are directly cytotoxic to target cells, and which influence the behavior of, and cause a focal accumulation of macrophages, lymphocytes and polymorphonuclear cells. This results in further release of lymphokinins which then exercise direct cytotoxic effects. Cell mediated hypersensitivity to microbial antigens and parasites, to protein and contact allergens, as well as the reactions to homografts, transplants, and autoimmune diseases, are all instances of delayed hypersensitivity. Cell-mediated hypersensitivity to bacterial products is probably responsible for the cavitation lesions associated with bacterial allergy, for human toxemias, and for the granulomatous skin lesions found in the tuberculoid form of leprosy. Delayed hypersensitivity however, is not always deleterious to the host. For example, many localized allergic responses to microbial agents may cause an accumulation of granulocytes, lymphocytes, macrophages, and immunoglobulins, all serving to eliminate bacteria from the affected areas. Of course, pharmacological hypersensitivity is the mode of action involved in the vaccination procedure. A number of laboratory tests are available for the evaluation of the responsiveness of the cellular immune system. These include T and B lymphocyte counts, lymph node biopsies, lymphocyte transformation studies using both phytohemagglutinin and specific antigens, the migration inhibitor factor (MIF) test and skin testing for delayed hypersensitivity.

The total number and percentage of T lymphocytes reflect the level of cell-mediated immunity. Normally, these cells represent approximately 60–70% of the circulating lymphocytes. Any significant increase or decrease in their number suggests a corresponding increase or decrease in the level of cell-mediated immunity. The response to nonspecific mitogens is thought to reflect the level of T cell activity in general, while the response to specific antigens may have a similar significance, or may reflect only the response to the particular antigen used.

Using phytohemagglutinin, the number of lymphocyte transformations are diminished when studied in patients with lymphoproliferative diseases, especially chronic lymphocytic leukemia. Impairment of the normal response to PHA has also been found in congenital thymic aplasia, the "Swiss" type of combined immunologic deficiency syndrome, Hodgkin's disease, sarcoidosis, lepromatous leprosy, Leishmaniasis and primary biliary cirrhosis. Lymphocyte transformation studies, using specific antigens, have been useful in diagnosing such allergic conditions as anaphylaxis (e.g., due to penicillin), immediate hypersensitivity to pollen, serum sickness due to sulfonamide, and delayed hypersensitivity to PPD. It is believed that skin testing with only 4 antigens (PPD, mumps, Candida, and varidase), could detect 90% of all delayed hypersensitivity reactions. In the unlikely event that the response to all 4 antigens is negative, de novo sensitization with dinitrochlorobenzene (DNCB) is the recommended procedure for unequivocally establishing the existence of defect in the cellular immune system.

2. *Humoral Immunity*

Although T lymphocytes are capable of reacting with antigen (antigen reactive cell, ARC) to form blast cells, they cannot form plasma cells nor can they produce antibody. This is the exclusive function of lymphocytes. These antibody forming cells (AFC) bear surface IgM and possibly IgD, as a monomer (either kappa or lambda), have Fc receptors for IgG antibody, and receptors for the third component of complement. The presence of immunoglobulins on the surface of B lymphocytes has been substantiated using immunofluorescent techniques, with reagents such as fluorescein-labeled anti-immunoglobulin, light chain. Surface receptors for IgG and C3 have been demonstrated by the formation of rosettes resulting from their exposure to red cells coated with IgG and C3 respectively.

B cells represent 25% of the human lymphocyte population. Certain highly polymeric antigens, such as pneumococcal polysaccharide, can directly stimulate B cells to produce antibodies. Smaller molecules are unable to do this, and must act as carriers by evoking T cell cooperation. It should be emphasized that the humoral antibody, and cellular immune systems are interrelated; the T and B cells function cooperatively, although the mechanism whereby the T helper cells influence B cell antibody production has not been clearly defined. The antigen-stimulated B cells give rise to mature plasma cells, which synthesize IgG, IgA, IgM, IgD and IgE immunoglobulins. These antibodies are specific for those antigens which elicited their production. A single plasma cell can secrete only one class of immunoglobulin, e.g., IgG (kappa) or IgG (lambda). Each of the five immunoglobulin classes plays a characteristic role within the body defense system: IgG protects the body fluid, IgA protects the body surface, IgE mediates immediate hypersensitivity, IgD appears to coat tumor B cells and is present on the surface of some cord blood lymphocytes, and protects the blood stream, and as it appears early in response to infection, it likely plays an important role in cases of bacteremia. The isohemagglutinins (anti A, anti B), and many natural antibodies to microorganisms, such as typhoid O antigen, are found in the IgM class.

When an antigen is either injected in high dosage or is weakly immunogenic, or when the immune response of the host is weak (as in immunosuppressive therapy), tolerance, rather than immunity, results. This phenomenon may affect both T and B cells. Tolerance in B cells is characterized by the suppression of antibody synthesis. The interaction of high doses of antigen with the immunoglobulin (antibody) receptors on the membrane surfaces of B lymphocytes results in their irreversible inactivation (clonal deletion). With regard to T cells, tolerance does not represent clonal deletion, but is, instead, an active process due to "suppressor T cells," i.e., lymphocytes which exert an inhibitory influence on other T or on B cells.

The immune response may also be inhibited by specific antibodies. This has been observed when tumors transplanted into the laboratory animals presensitized to tumor tissue, are not destroyed by the animals immune mechanism but instead, tend to proliferate. The causative antibodies are called enhancement antibodies. They apparently serve as physical barriers, preventing the attachment of other antibodies which are toxic to the tumor cells. If, on the other hand, the host's response to tumor antigen is to produce large amounts of cytolytic antibodies, with concomitant low production of enhancement antibodies, the tumor will regress. Understanding and controlling the balance between these opposing forces is an interesting and challenging problem for immunologists.

Patients with impairment of their humoral antibody response are highly susceptible to infection by both exogenous and endogenous, aerobic and anaerobic bacterial strains. These agammaglobulinemic individuals can effectively eliminate intracellular parasites (e.g., viruses, protozoa, fungi, rickettsiae, chlamydiae, tubercle bacilli) but are unable to destroy pyogenic bacteria such as staphylococci, streptococci, pneumococci, meningococci, and influenzae bacilli.

Tumor cells of the B type, which appear to be direct counterparts of normal B cells, have been shown to exist. These tumor cells are a probable result of an arrest of the normal cellular function of the immune system. These tumor B cells have immunoglobulins IgM and IgD (monoclonal, either kappa or lambda) on their surfaces, and their proliferation in patients with chronic lymphatic leukemia, myeloma, and Waldenstrom macroglobulinemia has been well documented. These patients also demonstrate an increased susceptibility to bacterial diseases as a result of defects in the production of antibody.

Many tests for humoral antibody response are available, including CBC and differential counts, cellulose acetate paper, quantitation of immunoglobulins, immunoelectrophoresis of blood and urine (for Bence-Jones proteins). Tests which measure specific antibody responses include those for; prior sensitization, isohemagglutinins (γM), polio virus, measles (γG), diphtheria (Shick), or scarlet fever (Dick test) (γG), and for de novo sensitization, e.g., Salmonella (γM); H (γG) antigens.

As was mentioned in the section on cellular immunity, the continuous stimulation of the host with multiple and repeated antigenic contact, may result in immunological injury. The example given was Type IV delayed hypersensitivity. In the humoral antibody system, 4 Types of effector mechanisms of such injury are recognized, all involving immediate hypersensitivity reactions. The first example, the Type I reaction (anaphylaxis) is mediated by IgE antibodies, called reagins, which sensitize mast cells, basophiles, and neutrophiles. Upon contact with antigen (allergen), such reagin-sensitized cells rupture, releasing pharmacologic mediators such as histamin, SRS-A, kinins and eosinophile chemotactic A factor. This response may be elicited by endotoxins of gram negative bacteria, and by a number of exotoxins, such as those from Staphylococcus aureus, Vibrio cholerae, Cl. septicum and welchii, and Shigella dysenteriae, where the products released include histamin, serotonin and catecholamine.

The type II reaction is mediated by cytotoxic antibodies. These antibodies are directed against antigenic cellular components, or antigens which have become intimately associated with cellular material. Leukopenia, neonatal hemolytic disease, and hemolytic anemia are a few examples of this type of reaction. Reaction Type III is mediated by immune complexes. Because AgAb complex formation is complement dependent, and because only IgM and IgG are effective in activating complement, this type of reaction is indirectly mediated by IgM and IgG antibodies. The AgAb complexes cause release of a chemotactic factor for polynuclears, which, in turn, release a lysosomal enzyme causing Arthus-type tissue damage. Acute, subacute, and chronic glomerulonephritis associated with bacterial, viral or malarial infections, erythematic skin nodules seen in the course of TB and coccidioidomycosis are examples of reaction Type III.

Finally, Type V, the stimulatory hypersensitivity response is mediated by non-complement-fixing antibodies which are directed against surface components of certain cells and which stimulate, rather than destroy, these cells. For example, the thyroid stimulating hormone (TSH) of pituitary origin is able to bind to its thyroid cell receptor due to the activation of the latter by an antibody—the long acting thyroid stimulator (LATS) which is probably an autoantibody.

Tests for immediate hypersensitivity reactions include the following: for Type I—basophilic degranulation, quantitation of IgE by radioimmunoassay, skin tests for allergens, and the Prausnitz-Kustner (PK) skin test; for Type II—measurement of cytotoxic antibody production such as in penicillin hypersensitivity; for type III—immune complex reaction is suspected serum precipitin antibody to milk and measurement of various autoantibodies; rheumatoid factor, antinuclear antibodies, antithyroglobulin antibodies, tissue biopsy for localization of γG and complement by immunofluorescence, warm agglutinins (37°C) for IgG antibody type, cold agglutinin (4°C) for γM, cold hemolysin (4°C) γG in tertiary syphilis. For Type V, determination of long acting thyroid stimulator (LATS) antibodies is performed.

Microbiologic Serology Procedures

A variety of in vitro techniques are available for the detection and measurement of antigen when the antibody is known, and vice versa. The following is a list of procedures available to the average clinical laboratory. More comprehensive procedures are available from the public health service laboratory.

1. *For detection of bacterial antigens*

Streptococci: Lancefield typing of groups A, B, C, D, G; fluorescent antibody techniques for group A and B.

Pneumococci: Capsular precipitation or Neufeld's Quellung reaction with polyvalent pneumococcus antisera on sputa, spinal fluids, other body fluids, or directly on bacteria isolated from any source.

Hemophilus: Slide agglutination or capsular swelling (Quellung) with Hemophilus serological types a, b, c, d, e, and f, done in spinal fluids.

Meningococci: Agglutination tests with groups A, B, C and D antisera.

Gonococci: Fluorescent antibody technique from clinical isolates.

Salmonella: Agglutination with the polyvalent O antiserum, and with antisera for groups A to G and the Vi antigen.

Shigella: Agglutination with Shigella dysenteriae, boydii, flexneri and sonnei antisera.

Arizona: Agglutination with Arizona antisera.

Brucella: Agglutination with Brucella abortus and melitensis.

Escherichia: In infants and young children (0–2 years of age) typing with OB sero groups: polyvalent OB and/or with specific sero O types 26, 55a, 86a, 111, 114, 119, 125a, 126, 127a, 128a. In both children and adults with acute diarrhea, sero types 0:124 and 0:148. Urinary strain O—1, 2, 4, 5, 6, 7, 9, 11, 18, 39, 75 and Alkalescens-Dispar O antisera.

Vibrio cholerae: Polyvalent antisera.

Treponema: VDRL qualitative and quantitative, automated charcoal reagin test or rapid plasma charcoal reagin test, FTA-ABS, FTA-ABS IgM (congenital syphilis), treponemal hemagglutination test (MHA-TP).

Counterimmunoelectrophoresis: This is an immunoprecipitation test developed recently for the detection in blood, urine, CSF and other body fluids, of small quantities of bacterial polysaccharides. This technique has been developed for the detection of pneumococci, hemophilus, meningococci, and Escherichia coli (K antigen).

Latex coated with antibodies: Useful in detecting cryptococcal antigen in spinal fluid and blood.

2. *For detection of antibodies to bacteria*

Febrile agglutinins: Three slide agglutination tests of questionable value when requested on a single specimen, and only of limited value performed on multiple specimens. Physicians may request any of these tests individually.

A. *Widal test:* Employs Salmonella O, H, and Vi antigens.

B. *Brucella test (Wright):* Agglutination with Brucella abortus antigen. Other procedures which may be requested include—tube dilutions, and tests for blocking antibodies (agglutination followed by Coomb's techniques).

C. *Weil-Felix:* Of value in endemic areas only. It is being replaced today by the use of rickettsial complement fixation tests.

Streptococcal infection: Four basic tests are available: the antistreptolysin (ASLO), the antihyaluronidase (AH), the antideoxyribonuclease B (anti-DNase B), useful in streptococcal skin infections and the anti-nicotinamide adenine nucleotidase (NA Dase), for serotypes 12, 4 and 49. Only 85% of patients with acute RF and documented streptococcal infection will show changing titer to ALSO (titers more than 250); the rest of 15% may show elevated titer to some of the other tests.

Fungal serology:

A. *Candidiasis:* Agar gel diffusion (or counterimmunoelectrophoresis) will detect 85% of systemic infections.

B. *Aspergillosis:* Agar gel diffusion with three antigens: A. fumigatus, A. niger and A. flavum. 2–4 strong bands indicate pulmonary aspergillosis, a moderate to weak single band may indicate a) early aspergillosis or b) asthma, related to aspergillosis hypersensitivity.

The Practical Application of Immunological Testing

In recent years, the employment of immunological techniques and criteria as aids in the diagnosis and treatment of disease has played an increasingly important role. Fully cognizant of this fact, the present day physician is faced with the problem of determining when, and to what extent a patient should be subjected to an immunologic profile. He must be guided in his choice by the underlying pathology and the symptomatology of the disease, and by the nature of the patient's general level of health.

As a noncomprehensive, yet useful guide, the following list of diseases, conditions, and situations are deserving of immunological attention:

A. *Impairment of humoral antibody responses and those of the biological amplification system*

Disorders of the spleen, associated with immune defects, disorders of phagocytic neutrophiles, complement deficiencies, defective (congenital or inherited) humoral immunity, dysgammaglobulinemias Types I–VII, immunological diseases in the newborn (isoimmunization), and those in the mother which affect the infant, and repeated infections in infants, children and adults.

Organ transplants; acute leukemias; excessive production of single cell line (the B cell) as in chronic lymphocytic leukemia, lymphosarcoma or other lymphoproliferative disorders; B2 cell line as in multiple myeloma, Waldenstrom macroglobulinemia or other plasma cell dyscrasias; all patients on immunosuppressive or radiation therapy; certain cancers with, or without, immunosuppressive therapy; serious bacterial infections unresponsive to antibiotic therapy; bacteremia with endotoxic gram negative shock. Immunologic mediated diseases to exogenous antigen: Type I anaphylactic, Type II cytotoxic, Type III AgAb complex mediated hypersensitivity, Type V stimulatory hypersensitivity. Immunologically mediated diseases to homologous antigen: transfusion, pregnancy, organ transplantation, tumor antigen. Immunologically mediated diseases involving autologous antigen-autoimmune disease.

B. *Diseases in which cellular immunity responses may be impaired*

Cellular immune deficiency syndrome, recurrent viral or fungal infection in children; immunologically mediated Type IV delayed hypersensitivity; patients with recognized cellular immune deficiencies such as tuberculosis, brucellosis, salmonellosis, leprosy, listeriosis, all fungal infections, Leishmaniasis, Toxoplasmosis, Pneumocytis carinii, and possibly latent and tertiary syphilis, prolonged treatment with X-ray radiation and immunosuppressive therapy and in all compromised host patients; certain malignant tumors (e.g., Osteosarcoma); patients with vaccinia, variola, herpes simplex and complicated measles.

Recently new concepts have been proposed for the clinical and immunologic analysis of patients with defects in cellular immunity and in certain infectious diseases. Clinical manifestations of these diseases is a function of the immunologic response of these patients rather than the variation in the infectibility or metabolic activity of the microorganism. With most of these diseases only a small portion of the patient population will develop clinical symptoms, while the majority seem to repel the infectious agents. It is believed that these individuals pass through a subclinical stage. Such a pattern has been shown to exist in leprosy, tuberculosis, Leishmaniasis and Cryptococcosis.

C. *Combined humoral and cellular deficiencies*

Primary defective combined immunity; effects of X-ray radiation and of immunosuppressive agents, effects of overgrowth of tumoral B cell line and depression of T cell line, excessive numbers of suppressor T cells.

Among the types of patients mentioned above, some may be categorized as "compromised hosts," i.e., those with lymphoproliferative malignancies, plasma cell dyscrasias, transplants, or those on long range immunosuppressive or radiation therapy, as well as other seriously ill patients. This type of patient, seen with increasing frequency in the modern hospital, is an excellent candidate for an immunological workup. Such an investigation would serve a two-fold purpose: first, it would exert a positive influence on the patient's diagnosis and therapy and second through widespread use, it would directly assist in the further evaluation and improvement of present procedures. As a minimum, the following procedures are recommended:

1) Tests for inflammatory responses: WBC and differential, sedimentation rate, C3, complement level, fibrinogen degradation products (FDP), and in specific cases, lymph node, bone marrow and rectal mucosa biopsies;

2) Tests for humoral antibody immunity: qualitative and quantitative immunoglobulin, cellulose acetate paper, immunoelectrophoresis, isohemagglutinin and antistreptolysin titers (low titer signifies poor antibody response), fungal serology (Candida and Aspergillus);

3) Tests for cellular immunity:

In vivo: intradermal skin testing with a series of four antigens which are commonly encountered in the environment—PPD, Mumps, Trichopyton and Varidase. All normal patients will respond to one or more of these antigens. Patients not responding to any antigen may be further evaluated by means of dinitrochlorobenzene (DNCB) skin test for their ability to develop a cell mediated immunity to a newly encountered antigen (active sensitization).

In vitro: total lymphocyte count, T and B lymphocyte quantitation or only T lymphocyte quantitation, and lymphocyte blastogenesis to phytohemagglutin or concanavalin A. Some laboratories may add testing for the migration inhibitory factor test (MIF).

This type of extensive testing performed on compromised and critically ill patients, provides vital information which can be used to determine whether such a patient falls into the so called "high risk" category. Two such high risk categories are now recognized: increased susceptibility to bacterial infection due to impairment of humoral antibody response, and greater susceptibility to fungal infections and diseases caused by intracellular parasites due to defective cellular immune responses. These patients should be monitored at frequent intervals during their hospitalization. Their management should be considered in terms of 1) treatment of the primary disease and its effect on immune function and resistance to disease; 2) treatment directly aimed at correcting immune deficiencies; and 3) treatment of immunopathic complications.

The last decade has seen revolutionary changes occurring in the practice of medicine. Many modern insights into the disease process are a direct result of the advances made in the field of immunology. Looking at our present day achievements, one may optimistically project the enormous promise that immunology holds for the future.

Acknowledgment

The author is indebted to Miss Sandra Samuels for many helpful criticism during the preparation of the manuscript.

Selected References*

D. L. Nelson: Macrophages and Immunity. American Elsevier Publ. Co., 1969.

L. Mudd: Infectious Agents and Host Reactions. W. B. Saunders Co., Philadelphia 1970.

J. L. Turk and A. D. M. Bryceson: Immunological Phenomena in Leprosy and Related Diseases, Adv Immunol 13:209, 1971.

J. A. Bellanti: Immunology. W. B. Saunders Co., Philadelphia 1971.

B. R. Bloom and P. R. Glade. In Vitro Methods in Cell Mediated Immunity. Academic Press, Inc., New York 1971.

P. L. Cawley, M. G. Penn, R. Nakamura, E. Tucker, L. Deodhor, and V. Agnello: Clinical Immunology and Immunochemistry, Am Soc Clin Path, Chicago 1972.

C. R. Williams and H. H. Fudenberg: Phagocytic Mechanism in Health and Diseases, Intercontinental Medical Book Corp., New York 1972.

M. Samter. Immunological Diseases V. I and II. Little Brown & Co., Boston 1972.

F. H. Bach and R. A. Good: Clinical Immunobiology VI. Academic Press, New York 1972.

B. Davis, R. Dulbeco, H. N. Eisen, H. S. Ginsberg, and W. B. Wood: Microbiology, Harper and Row, N. Y. 1973.

C. J. O'Connell: Laboratory Diagnosis of Infectious Diseases. Medical Examination Publication Co., Inc., New York 1973.

R. N. Rose, F. Milgrom, and C. J. Oss: Principles of Immunology, Macmillan, N. Y. 1973.

J. H. Humphrey and R. G. White: Immunology for Students of Medicine. Blackwell Scientific Publishers, Oxford 1974.

P. G. H. Gell, P. P. A. Coombs, and P. Lachmann. Clinical Aspects of Immunology. Blackwell Scientific Pub., Oxford 1974.

B. L. Gordon: Essentials of Immunology. F. A. Davis Co., Philadelphia 1974.

B. A. Briody and R. E. Corlis: Microbiology and Infectious Diseases. McGraw-Hill Book Co., N. Y. 1974.

J. T. Barrett: Textbook of Immunology, C. W. Mosby Co., N. Y. 1974.

I. Roitt. Essentials of Immunology. Blackwell Scientific Publication, Oxford 1974.

*Detailed references may be obtained by writing to the author.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 1, January-February, 1977
Printed in U.S.A.

Historical Survey of Tests to Determine Bacterial Susceptibility to Antimicrobial Agents

MICHEL LAVERDIERE, M.D.* AND L. D. SABATH, M.D.

The clinical importance of determining the susceptibility of bacteria to various antibiotics cannot be overemphasized. Some extremists have suggested it is more important to know the "antibiogram" of a clinical isolate than its speciation. Although many medical microbiologists and students of antibiotic susceptibility testing would probably agree that that statement is true only in some instances, all would probably agree that susceptibility testing is of considerable clinical usefulness.

It has been, and is, a salient feature of Stanley Schneierson's scientific career to pinpoint key problems in medical microbiology and come up with practical solutions. His introduction of the "disc dilution" system, in 1951, for distributing antibiotics is a good example of this, and current interest in applications of this technique is a testimony to his ingenuity and farsightedness. Its place in the historical evolution of various techniques for susceptibility testing follows.

Agar Diffusion Methods

The diffusion methods are based on the ability of an inhibitory substance to spread uniformly from its origin point (which may be a disc, cylinder, hole or gutter) into a solid medium. As the inhibitory agent spreads away from its origin the concentration in the medium proportionately decreases. The growth of organisms will occur at those locations where the concentration of antibiotic in the agar is not high enough to inhibit the inoculated organisms. Various diffusion methods have been described.

Diffusion from a gutter: In 1922 Fleming reported on the bacteriolytic activity of elements found in tissues and secretions. He used an in vitro system, designed to show the diffusion into the agar of the inhibitory substance (1). He removed a small portion of the agar from an ordinary agar plate, and filled the cavity with the material rich in "lysozyme"; a drop of liquid agar was placed on the material and allowed to solidify. Liquid agar was then poured all over the plate to make a thin layer over the original surface. The whole surface of the medium was then seeded with bacteria. The inhibition he observed was due to the penetration into the agar of an inhibitory substance, lysozyme. Fleming subsequently described (2, 3) a technique in

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From the Section on Infectious Diseases, Department of Medicine, University of Minnesota Medical School, Minneapolis, Mn. 55455.

*Research Fellow of Quebec Health Research Council, Canada.

Requests for reprints should be sent to: Dr. L. D. Sabath, Box 219 Mayo Memorial Building, University of Minnesota, Minneapolis, Mn. 55455.

which a block of agar was removed and replaced by a mixture of agar and inhibitory substances. In 1929 when he reported his classic communication on penicillin, Fleming (4) used the same technique. The penicillin was embedded in culture medium across an agar plate, and the various "microbes" were streaked at right angles. The sensitivity of the microbes were estimated by the distance over which growth was inhibited.

The same technique was also used to detect the appearance of penicillin resistant staphylococci (5,6) and to study the sensitivity of bacteria to streptomycin and sulfathiazole (6–8).

Diffusion from a hole (the agar-hole plate method): Reddish (9), in his paper on methods of testing antiseptics, was possibly among the first to describe the agar-hole method, although Fleming had mentioned that technique 7 years earlier (1). The method consisted of placing a sterilized glass stopper 1.5 cm in diameter at the center of a Petri dish, immediately after the melted agar had been poured. Once the agar solidified, the glass stopper was delicately removed. In a 1939 study Rose et al (10) looked for the variables that could possibly modify the results obtained with the agar-cup method, and described a standardized agar-hole technique.

In 1951 Erlanson (11) conducted an extensive study of the agar-hole method, focusing mainly on the problems of the medium, the size of the inoculum, the time of incubation, the criteria for classification, the results, and the mechanism of the agar-cup diffusion method. He determined the inhibitory activity of 5 different chemotherapeutic agents against 7 different bacterial species. He compared his results with a serial tube dilution method, using a liquid medium, and concluded that the agar-hole method was suitable for routine sensitivity tests. But in the following years it was felt that the agar-hole method was too time consuming to be used in the routine laboratory.

Diffusion from a cylinder (cylinder-plate method): The cylinder-plate method had been derived from an assay technique for penicillin (12, 13). The solutions to be tested are placed in small cylinders, generally of glass (later metal) which are placed on the surface of the inoculated agar medium. The application of this technique in the testing of sensitivity to chemotherapeutic agents, although mentioned, (12) has never been widely used (14).

Drop method: In this technique drops of the chemotherapeutic agent are placed on the surface of the agar plate. Fleming first used this technique (4) to show the inhibition of Gram-negative cocci by streptococci and pneumococci in sputum or saliva. He found that 5 or 6 drops of penicillin inhibited the Gram-positive cocci which permitted Gram-negative cocci in sputum to grow. That same principle was used by Haxthausen in 1941 (15) in the description of his simplified method for cultivation of streptococci from skin lesions containing both streptococci and staphylococci. Once the surface was inoculated with the pus specimen, he added a drop of crystal violet 1% on the middle of his culture plate. He obtained a circle of complete inhibition, with the streptococci appearing in the ring-shaped zone, surrounded by the colonies of staphylococci. In the following year Hagerman (16) studied the resistance of gonococci with a similar method.

In 1944 (17) Thomas et al reported a procedure in which the test organisms were seeded in the agar. They then showed, using a 4 mm loopfull drop method, that there was a direct relation between the dimension of the zone of inhibition and the concentration of penicillin applied. They finally suggested that the growth inhibition zone produced would be an inverse function of the resistance of the test organism. The following year the same group, (18) using various strains of staphylococci obtained from suppurating infections, established the relation between the zone of inhibition obtained with their technique, and the amount of penicillin inhibiting growth of the same organisms in nutrient broth. They then described in detail their technique and suggested its use for evaluating resistance of bacteria to penicillin. They also indicated the size of the growth zones of inhibition required to determine the resistance or sensitivity of the test organisms, and also the expected clinical response.

But such a technique was cumbersome and hardly usable for routine determination of bacterial sensitivities.

Gradient plate technique: In 1952, while doing studies on bacterial cross resistance to a large variety of antibiotics, Szybalaski (19) set up a new method to isolate resistant strains. He prepared an agar with a gradual proportional increase of the antibiotic concentration along one horizontal axis. A layer of agar containing antibiotic was poured over an agar slant already covering the entire bottom of the Petri plate. The antibiotic could then diffuse downward and the concentration was in proportion to the ratio of the thickness of the agar surface. In the following years, Braude et al (20) reported a study adapting the use of the gradient plate for routine determinations of bacterial sensitvity to antibiotics in the clinical laboratory. Using bacteria isolated from human infections,and comparing their results with the sensitivities obtained by the standard agar plate dilution method, they found good correlation with all the antibiotics except erythromycin. They therefore described the gradient plate as "perhaps the best clinical method for testing sensitivities to antibiotics." But the test required many plates to test a single organism against several agents and was not widely used on a routine basis.

Diffusion from tablets: In 1947, Hoyt et al (21) described a method to determine sensitivity of microorganisms that used compressed tablets, into which the drug was incorporated. The agar plates were streaked heavily with the organisms, and the tablets were thereafter dropped on the agar surface with forceps. After incubation, inhibition was shown by sensitive organisms. No measurement of inhibition zone was suggested. But when the tablets became commercially available, the same group of workers (22) then prepared tablets indicating the relative sensitivity of bacteria in the range of concentration observed clinically in blood and urine.

Although the tablet method was a quick and accurate method, (23) and commerically produced tablets were reliable, (24) a W.H.O. report indicated (25) that the tablets were slow in releasing the antibiotic, and that they may per se inhibit the bacterial growth.

But in 1972 Casals and Pedersen, (26) using the same technique, showed that the new tablets themselves (neo-sensitabs) had no inhibitory effect on the bacterial growth, and that after a prediffusion period, the diffusion of antimicrobial agents in a solid medium did correlate with results using paper discs.

Diffusion from filter paper strip: An agar diffusion technique, using a filter paper strip impregnated with six different antibiotics was suggested in 1955 by Czerkinsky et al (27). Once the strip placed on the surface of an agar plate one-half of the plate on one side of the strip was swabbed with a suspension of the test organism, and the other half was swabbed in a similar way with a suspension of a standard strain. In doing so, the degree of resistance was not based on the absolute value (in mm) of the zone of inhibition but on the relation between two zones, one of the test strain, and the other of the reference strain. Although that method was shown to be as accurate and sensitive as the disc method described by Ericsson (28, 29) and used a standard strain (serving as control of the intrinsic variations in strips), media and technique, it did not gain much popularity.

Diffusion from filter paper discs: The use of filter paper discs soaked with solutions of the chemotherapeutic agent and placed on the surface of seeded plates was first described for assays of antibiotics (30–32) and subsequent modifications of that technique were used for sensitivity tests. The radial streak method (33, 34) was one of the early modifications described. On the bottom of the Petri plate a central circle 15 mm in diameter was drawn with radial lines extending to the edge of the plate dividing it into six sectors. Into each sector different bacterial specimens were streaked from the center to the edge of the plate. A disc of filter paper was impregnated with an antibiotic solution and placed in the center of the plate. The result was judged by comparing the size of the zone of inhibition with that produced by a test strain of known susceptibility under similar conditions. Bondi in 1947 (35) described a routine method using filter paper discs saturated with a known amount of antibiotic; these were placed on the surface of a freshly inoculated plate. Several discs containing different antibiotics could be applied to a single plate at the same time. After incubation, the zone of inhibition around each disc was noted. Bondi recognized that the zone sizes were related to both the concentration and diffusibility of the antibiotic, and also to the relative susceptibility of the organism.

The misunderstanding of this basic principle led to modifications of Bondi's methods which in turn resulted in confusion. A number of workers suggested that the amount of antibiotic placed on the disc should correspond to levels attainable in blood. They then defined sensitivity as a clear zone of any size surrounding the disc (36, 37).

Multidisc (37, 38) methods were also developed, based on the desire to establish a closer clinical correlation with other in vitro methods. Three discs containing high, intermediate and low quantities of antibiotics were used. Once again, the diameter of the zone of inhibition was totally ignored. The organisms could be classified as sensitive, moderately resistant, or resistant depending on which discs produced zones of inhibition (38, 39). But the clinical correlation was poor. Modification of the disc content was then suggested as a possible way to have a better therapeutic guide.

With such standardization, a strain giving a zone of inhibition of at least 10 mm (40) or 15 mm (41) would be considered as sensitive, and treatable in clinical situations with usual dosages.

In 1959 Bauer et al (42) reverted to Bondi's basic principle. They reported a study on the sensitivity of 2,000 strains of staphylococci and showed the practical and scientific superiority of the single high-content disc. They also pointed out again the importance of quantitation of the zone of inhibition. The following year, the same group reported additional experience in a study on the sensitivities of 100 strains of staphylococci, against five different antibiotics (43). In that study they also showed a better correlation between their results and the clinical response. In 1966, Bauer, Kirby, Sherris and Turck (44) gave full details of their technique and insisted on the standardization and the easy routine application of it. Their technique was thus a disc diffusion technique, using a single high content antibiotic disc for each antibiotic. The sensitivities of the organisms were based on the dimension of the zone of inhibition.

Stressing the fact that the Kirby-Bauer method requires only a difference of 1 millimeter to separate a susceptible from an intermediate organism, Rose and Snyder (45) suggested a technique that eliminated the need for zone diameter measurement. The "all or none" antibacterial disk tests was described using a synthetic medium 2 mm deep, a 1.5×10^6 bacteria/ml inoculum, and an antibiotic disc of lower potential. The group of organisms of intermediate sensitivity was then eliminated. Using E. coli the method yielded reliable results in 98% of strains, but the technique had not shown comparable accuracy with other rapidly growing bacteria.

Because of the increasing number of organisms and antibiotics tested in diagnostic laboratories, zone size charts were proposed as a way to simplify the measurement and interpretation of zone diameters (46, 47, 48).

The method described by Kirby et al, was also felt to be too time-consuming, and different modifications were subsequently proposed. Barry et al (49) suggested a more practical way to standardize the inoculum, and to inoculate the test plates. With the Kirby-Bauer method the inoculum was standardized by adjusting the turbidity of an actively growing broth culture to match with that of a $BaSo_4$ standard (McFarland standard). Mueller-Hinton agar plates were then inoculated with cotton swabs moistened in this suspension. Barry et al suggested an alternative method for standardizing the inoculum, based on the observation that bacteria multiply in broth cultures until a maximum cell concentration is reached, after which, with further incubation, the number of viable bacteria remains stationary. The time required to reach the stationary phase depends on the size of the inoculum and on the volume of broth inoculated. They therefore suggested using 0.5 ml of broth, inoculated with 5 to 10 colonies and allowed to incubate 4 to 8 hours. A 0.001 ml calibrated loopful broth was then mixed in a tube of melted agar, which was then mixed and spread over an agar surface in a Petri dish. Once the thin layer of seeded agar hardened the discs were placed on the surface of it. The zones of inhibition were nearly identical to those obtained with the standardized Kirby-Bauer and they were also more clearly defined. Other methods with this "overlay" method of inoculation were suggested with the intent of having more evenly spread inoculum and zones that would be easier to read. The flooding technique was proposed, but was shown to form irregular zones resulting from the draining step (50). Some also felt this was an unnecessary risk for the manipulator, when working with highly pathogenic strains (51). The cotton swab spreading technique was proved accurate (51, 52) and the use of rotary plater devices (53) produced even more uniformly spread inoculum and the resulting zones of inhibition were easier to read.

Because of the many possible errors that could be made while working with the disc diffusion method, controls with standard sensitive strains were felt to be necessary. In 1968, Stokes described (54) a method in which the zones of inhibition of the test organism could be compared with those of a known sensitive control strain each produced by the same disc in the same Petri plate. In using such procedures, a permanent quality control of the technique was set for each plate, and the variations that could occur in the material used could be easily detected. But such a technique was cumbersome and permitted testing of only 4 different antibiotics on each standard (100 mm) plate. Pearson and Whitehead (55) modified Stoke's method, using a rotary plater and could test up to six antibiotics with each 9 mm Petri dish. Following Stoke's suggestion, the daily use of reference strains was then suggested by the International Study in 1971 (50). That recommendation was rapidly endorsed (56, 57).

The modifications described by Bondi (35) (and later by Kirby, Bauer, Sherris and Turck) required incubation for 6 to 18 hours prior to being interpreted. The emergency nature of some clinical situations prompted a handful of workers to look for modifications that could reduce the period of incubation. In 1956 (58), Pital et al described a method in which the reduction of resazurin provided results after 1½ hours incubation but the correlation with standard techniques was poor. Melia et al (59) using a previously described principle (60, 61) based on the hemoglobin reduction by viable bacteria showed a 98.7% correlation between their technique and the standard Kirby-Bauer method. Only 4 hours of incubation was necessary. Boyle et al (62) reported, in 1973, a modified Kirby-Bauer disc susceptibility method that gave results after 6–7 hours of incubation at 37°C. They vaporized an aqueous solution of tetrazolium to enhance delineation of areas of growth and zones of inhibition. They used two American Type Culture Collections (ATCC) reference strains and showed a significant correlation between their technique and the Kirby-Bauer technique. Routine application has remained limited.

In the Kirby-Bauer method the zone size is usually converted to a sensitivity category. Indicating that errors in that conversion can occur once in every 12 reports, Petralli and coworkers (63) suggested that conversion be made by a computer. Later, computerized systems were used to measure the zones of inhibition and to convert them to appropriate sensitivity categories in just one operation (64).

Dilution Techniques

The purpose of dilution techniques is to determine the minimum inhibitory concentration (MIC), the lowest concentration of antibiotics that inhibit visible growth. The basic technique is to expose bacteria to various known concentrations of antibiotic usually serial two-fold in dilution, solid or liquid medium, and then incubate as is necessary.

Agar dilution methods: Because the diffusion of sulfonamides was inconstant and gave incoherent in vitro sensitivity results, workers in the early 1940's used agar dilution techniques to obtain more reliable results (65, 66, 67, 68). Subsequently, the use of those techniques was extended for testing other antibiotics (11, 69, 70 71, 72).

In 1951, Jackson and coworkers (39) described in detail an agar dilution method. With known concentration of antibiotic incorporated in the agar, each plate was divided in small square sections, and the inoculation was made by streaking the content of a 1 mm calibrated loop over each square. The inoculation was then cumbersome and time-consuming.

In 1959, Steers et al (73) suggested a more rapid method of inoculation, using an inocula-replicating apparatus derived from a technique used by the Lederbergs (74) to select bacterial mutants. The apparatus consisted of a sliding plate which held an inoculum reservoir (with 36 wells) and one Petri dish (containing the drug in an agar medium). A fixed aluminum head possessing 36 rods corresponding to the 36 wells in the inoculum reservoir was suspended above and activated downward, by pressing on a piston. A spring located within the piston automatically set the replicating head in its initial position when pressure on the piston was released. To use the apparatus, the aluminum rods were first lowered into the inoculum reservoirs with a single stroke, each rod dipping into its respective well, and then lifted. The Petri dish containing agar and antibiotic was then slid under the aluminum head, and inoculated with 36 different cultures with a single stroke. Hence, for each single manipulation of the apparatus, 36 bacterial isolates could be inoculated at the same time.

In the following years, the same group of workers showed the superiority of their techniques over the previously described inoculation technique for agar dilution method (75). They also reported adequate correlation between their results and either tube dilution or disc diffusion results (75, 76). Since its description, the Steer's method has been widely used. Its reliability has been endorsed by the international Collaboration Study (50), and most workers consider it the most reliable method for determining an MIC.

A more rapid agar dilution sensitivity test was suggested in 1965 by Mahoney et al (77). The criterion of sensitivity was based on the inhibition of microcolony formation on the surface of agar plates. Results were available after only 4 hours of incubation, but the necessity to observe each antibiotic plate with a microscope and the poor correlation with the standard techniques contributed to its failure to be adopted.

Tube dilution (broth dilution) methods: Although previously described by Fleming (4), Rammelkamp and Maxon (78) first described the method which forms the basis for the tube dilution (broth dilution) tests in use today. Their work was initiated in a study of the resistance of Staphylococcus aureus to the action of penicillin. Rammelkamp and Maxon used a twofold dilution technique. Other workers used smaller dilution steps in order to get a greater accuracy (79, 80), or techniques not based on serial dilutions at all (81). But these techniques as that of Rammelkamp et al were time-consuming and not usable on a large scale as described. Some modifications were suggested to make its use practical. A number of workers suggested limiting the test to only a few dilutions covering concentrations of practical and clinical importance (82, 83, 84). Others proposed methods, using a lyophilized sample of antibiotic in nutrient (85) or already diluted concentrations maintained in a frozen state until ready to use (84).

Schneierson proposed in 1951, "a simple, rapid disc-tube method for testing antibiotic susceptibility of strains belonging to several potentially pathogenic bacterial species" (86). The method was based "on the ability of strains to produce a good visual growth in a suitable liquid medium with a moderate sized inoculum within an average of 4 to 6 hours, and also, on substitution of commercially available filter paper antibiotic solutions and dilutions employed in the tube dilution test." Schneierson performed simultaneous sensitivity determinations of 458 organisms isolated from pathologic materials, using the conventional tube and his disc-tube methods. By reporting his results in terms, "index of resistance," obtained by comparing the minimum amount of antibiotic necessary to inhibit the growth of the test organism with the amount required for a sensitive standard organism, he reported 70% to 79% overall correlation between the two methods. Schneierson's disc-elution technique has been revived and recently experienced an increased popularity with its application to automated systems (87, 88). The Autobac I (89) system is one such system. The system involves an automated instrument for the comparison by fixed angle light scattering to detect growth in a control broth and in broth containing antimicrobial agents eluted from discs in a special disposable plastic multichambered cuvette. The instrument automatically reads light scattering, calculates and points out the results. Overall agreement between this automated technique and the standardized Kirby-Bauer methods was approximately 90% (90, 91). In one of these studies (90) more than one-half of the discrepancies were minor. In that same study there was 90% agreement between "Autobac" results and agar dilution results, whereas the overall agreement between the diffusion test and the dilution method was 91%. In another study (92) 78% of complete agreement was found over 2700 determinations between the Autobac I results and an agar dilution method. It was suggested that the lower percentage of agreement might be explained by variation of certain elements (media, pH, inoculum, etc.) in the disc-elution method. The automated disc-elution method provides semi-quantitative data on bacterial susceptibility which are rapidly obtained and which seems to be reliable (92).

Other modifications of the standard tube dilution technique have been previously suggested to provide more rapid results. Sellers et al (93) in 1969, used the principle of hemoglobin reduction by growing bacteria, and obtained results after 45 minutes of incubation. They obtained 87% agreement between their results and "routine sensitivity plate." Berkman et al (94) in 1970 reported a method detecting sensitivity of S. aureus to penicillin that could be detected in 3 minutes after the addition of the antibiotic. The method was based on the change of scattering angle, after addition of various penicillin concentrations of broth medium containing growing staphylococci.

But determination of a quantitative susceptibility of organisms, towards many antibiotics, using tube dilution method, was still limited by the amount of time and work it required. The application of microtechnique to antibiotic susceptibility testing was then introduced.

In 1965, Koch and Kaplan (95) described a microtechnique where they could test the sensitivity of organisms to 8 different antibiotics in the same experiment. Their system utilized a device with 25 holes radially placed in a 10 cm Petri plate in 8 series of 3. The last hole was placed in the center of the Petri plate, and was used as a growth standard. In the antibiotic containing cavities, 0.05 ml of drug solution was dried in vacuo. Only 3 concentrations of a drug were used. These concentrations were selected to correspond to levels achievable in vivo. In use, 0.2 ml of a 5×10^5 colony forming units (CFU/cc inoculum was dispensed in each cavity. After incubation, growth was determined by the formation of a sediment in the tip of the cavity. Their results were comparable with those obtained from a standard tube dilution test. In 1966, Marymount (96) described the application of a Viral Serological technique (97) to antibiotic susceptibility testing. He used a disposable plastic plate containing 8 horizontal rows, 12 wells, and calibrated droppers, and spiral loops (98). Serial twofold dilutions of 8 antibiotics were performed in the same operation. A 95% agreement with an acceptable deviation of ± 2 dilutions, was shown between the microtechnique results and those obtained with a standard tube dilution. Harwick in 1968 (99), and Chitwood (100) in 1969, used the same micromethod on 76, and 179 determinations showed correlations with standard tube dilution of 92.5% and 94% for a ± 1 dilution deviation. Gavan (101) showed that the reproducibility of the microtechnique was 94.8% whereas that of the macrodilution was 99.1%.

Automation was soon introduced in the microdilution susceptibility testing (102–106). Correlations between the automated techniques and the macrodilution was shown to be 87% to 91% (102, 105), and the reproductibility was 95% (104–106). Finally, in order to facilitate the reading, some workers suggested the incorporation of indicators into the medium (107, 108).

Other Susceptibility Testing Methods

Prediffusion technique: Rolinson and Russell (109, 110) suggested "a test method which retains the simplicity of the paper-disc method but which enables organisms to be tested directly for susceptibility to known concentrations of antibiotic in agar." The method was based on the observation that when a thin layer of agar was covered with paper impregnated with antibiotic, diffusion of the latter was rapid, and essentially uniform distribution of the antibiotic in the agar was achieved. In this way, known concentrations of antibiotic in the agar could be easily achieved. After removal of the paper from which the antibiotic had diffused, the agar surface could be inoculated with the test organism. In this experiment Rolinson and Russell showed that after 4 hours of diffusion at 25°C most of the antibiotic had passed from the paper into the agar. The antibiotic concentration in the agar of 15 various antibiotics range from 81% to 103% of the theoretical calculated concentration. The minimal inhibitory concentration obtained with the new method and a standard agar dilution technique showed very few discrepancies. The authors finally suggested that commercially prepoured agar in plastic trays containing 4 rows of 8 wells, each measuring 10 by 15, and 3 mm in depth, could be made available and facilitates the use of their method in routine practice. In addition to prepoured plastic trays, paper impregnated with adequate concentrations of antibiotic could be commercially supplied thus permitting a routine susceptibility test which is no more time-consuming than the conventional disc method. So far little application of Rolinson's technique to routine susceptibility testing have been described.

Microcalorimetric method: The microcalorimetric method is based on the natural production of heat by any viable organism. The sensitivity of bacteria to antibiotics could then be tested on the basis of continual increase in metabolic heat, unchanging metabolic heat, or decreasing metabolic heat. Binford and coworkers (111) using such a system showed up to 87% agreement of their results with results obtained using an agar diffusion method. The distinctive features of the microcalorimetric method were that bacteriostatic and bacteriocidal drugs could be distinguished, that results could be obtained 12 to 24 hours sooner than the disc diffusion method and that it could be fully automated.

Radiospirometric methods: These methods are based on the measurement of ^{14}C- released by the bacteria as a result of their metabolism. In 1960, Hein et al (112) described a technique in which a liquid growth medium with ^{14}C-glucose was seeded with bacteria. Antimicrobial agents were then introduced in some of the media. As inhibited cells were yielding less CO_2 than non-inhibited cells, the collection and comparison of the CO_2 evolved from antibiotic and antibiotic-free controls could be used to determine the sensitivity of the bacteria. More recently, Moser et al (113) using the same basic principle with a microchamber suspended in a small liquid scintillation vial described a technique to assay sensitivity of slow growing microorganisms.

Impedance method

Measurement of bacterial growth can be correlated with changes in the growth medium resulting from biochemical events in the metabolism of the organism. Some of the events change the electrical impedance of the medium. Hence, growth—and inhibition of it (as with antibiotics)—can be monitored by measurements of impedance. No extensive study comparing this method of sensitivity testing with more conventional methods reached us.

Chemiluminescence: A novel approach to detecting growth, or the absence of it, has been explored by the Dupont group. By using the sensitive firefly-luciferin system to detect very small amounts of adenosine triphosphate (ATP) they have been able to detect small increments of bacteria growth. Although their first efforts of a clinical application were directed primarily at such problems as blood and urine cultures, more recent efforts have been to detect inhibition of growth by antibiotics in sensitivity tests. Extensive comparisons of this new method with established ones have not been published yet (Gutekunst, personal communication).

Change in surface charge method: One of the earliest antibiotic-induced changes on bacteria is a change in the surface charge (114, 115). This change only occurs if the organism is sensitive. Because the change occurs early, rapid (possibly within minutes) determination of sensitivity is possible by this method. A practical clinical application of this technique awaits the development of a procedure for detecting change in surface charge that would be more convenient than the present cumbersome one of cell electrophoresis—all in which the timed movement of bacteria in an electrical field (water cooled) is observed through a microscope.

Laser beam method: Another early surface change produced by antibiotics when sensitive bacteria are exposed is a change in the way they reflect a laser beam. For several years, the Spectrum firm in California has been conducting tests of the possible utility of a device to detect changes in a signal produced by the reflection of the laser beam. In its present form, the device has not produced data that correlates well with conventional methods (C. Thornsberry, personal communication).

Summary and Conclusions

Numerous, sometimes ingenious, methods have been developed by many workers all over the world to test bacteria for their susceptibility to antibiotics. The simplicity and "relative" freedom from some types of errors are major factors that have made the disc diffusion method the most popular one in the United States. However, the necessity to use antibiotics with a narrow toxic: therapeutic ratio (such as gentamicin and tobramycin) have made us feel a method that yields *quantitative* data on the sensitivity of bacteria is needed when use of those antibiotics is contemplated. The combined use of a quantitative sensitivity test with measurements of serum (and other fluid) levels of antibiotic (116) during treatment are needed to add approproate precision to antibiotic therapy in those situations.

References

1. Flemming, A.: On a remarkable bacteriolytic element found in tissues and secretions, Royal Soc of London Proc (Series B) 93:306–317, 1922.

2. Fleming, A.: Further observations on a bacteriolytic element found in tissues and secretions, Royal Soc of London Proc (Series B) 94:142, 1922.
3. Fleming, A.: A comparison of the activities of antiseptics on bacteria and on leucocytes, Royal Soc of London Proc (Series B) 96:171–180, 1924.
4. Fleming, A.: On the antibacterial action of cultures of a penicillium with special reference to their use in the isolation of B. Influenzae, Br J Exp Pathol 10:226–236, 1929.
5. Voureka, A. and Hughes, H. W.: Frequency of penicillin resistant staphylococci, Brit Med J 1:395, 1949.
6. Barber, M. and Whitehead, J. E. M.: Bacteriophage types in penicillin resistant staphylococcal infection, Brit. Med., J., 2:565–569, 1949.
7. Fleming, A.: Proc. Royal Society of Medicine—Section on therapeutics and pharmacology,
8. Colebrook, L. and Francis, A. E.: Varying sensitivity of haemolytic streptococci to the sulphonamides, J Path and Bacteriol 53:155–156, 1941.
9. Reddish, G. F.: Methods of testing antiseptics, J Lab Clin Medicine 14:649–658, 1929.
10. Rose, B. S. and Miller, R. E.: Studies with the agar-cup plate method: I: A standardized agar-cup plate technique, J Bact 38:525–537, 1939.
11. Erlanson, P.: Determination of the sensitivity in vitro of bacteria to chemotherapeutics agents with special references to routine test. Acta Pathol Microbiol Scand Suppl 85:1–162, 1951.
12. Abraham, E. P., Chain, E., and Gardner, A. J. et al: Further observations on penicillin, Lancet 241:177–189, 1941.
13. Heatley, N. G.: A method for the assay of penicillin, Bioch J 38:61–65, 1944.
14. Petersdorf, R. G. and Plorde, J. J.: The usefulness of in vitro sensitivity tests in antibiotic therapy, Ann Rev of Medicine 14:41–56, 1963.
15. Haxthausen, H.: Eine vereinfachte kristallviolettmethode, zur, zuchtung von streptokokken von der haut, Acta Derm Venereol 22:262–267, 1941.
16. Hagerman, G.: Studies on the chemoresistance of gonococci, Acta Pathol Microbiol Scand Suppl 46:1–180, 1942.
17. Thomas, A. R., Levine, M., and Vitagliano, G. R.: Simplified procedures for ascertaining concentration of a bacterial susceptibility to penicillin, Soc Exp Biol and Medicine Proc 55:264–267, 1944.
18. Levine, M. and Thomas, A.: The inhibition zone technique for determination of bacterial resistance to penicillin, J of Lab and Clin Med 30:883–890, 1945.
19. Szybalski, W.: Gradient plate technique for study of bacterial resistance, Science 116:46–48, 1952.
20. Braude, A. I., Banister, J., and Wright, N.: Use of gradient plate for routine clinical determinations of bacterial sensitivities to antibiotics, Antibiotics, Annual 1954–1955, 1133–1140.
21. Hoyt, R. E. and Levine, M. G.: A method for determining sensitivity to penicillin, and streptomycin, Science 106:171, 1947.
22. Hoyt, R. E. and Levine, M. G.: Comparison of tablets and solutions on measurement of bacterial sensitivities to antibiotics, Am J Clin Path 20:865–869, 1950.
23. Lund, E., Funder-Schmidt, B., Christensen, H., and Dupont, A.: Sensitivity test with the tablet method, Acta Pathol Microbiol Scand 29:221–224, 1951.
24. Lund, E.: Resistance determinations with tablets, containing various amounts of active substances, Acta Pathol Microbiol Scand 3:278–284, 1953.
25. World Health Organization Tech. Report Service 210:1–24, 1961.
26. Casals, J. B. and Pedersen, G. O.: Tablet sensitivity testing: A comparison of different methods, Acta Pathol Microbiol Scand (Sction B) 80:806–816, 1972.
27. Czerkinsky, G., Diding, N., and Ouchterlony, O.: New method for determination of bacterial sensitivity to chemotherapeutic agents by means of paper strips, Scand J Clin Lab Invest 7:259–263, 1955.
28. Ericsson, H., Hogman, C., and Wickman, K.: A paper-disc method for determination of bacterial sensitivity to chemotherapeutic and antibiotic agents, Scand J Clin Lab Invest 6:(Suppl 11) 1951.

29. Mollstedt, B.: A comparison between two diffusion methods for determination of bacterial sensitivity to antibiotic agents, Scand J Clin Lab Invest 9:15–20, 1957.
30. Vincent, J. G., and Vincent, H. W.: Filter paper disc modification of the Oxford cup penicillin determination, Proc Soc Exp Biol Med 55:162–164, 1944.
31. Sherwood, M. B., Falco, E. A., and Debeer, E. J.: A rapid quantiattive method for the determination of penicillin, Science 99:247–248, 1944.
32. Loo, Y. H., Skell, P. S., Thornberry, H. H., et al: Assay of streptomycin, by the paper disc plate method, J Bact 50:701–709, 1945.
33. Mohs, F. E.: A simple quantitative test for the penicillin sensitivity of bacteria: The radial streak method, J Lab Clin Med 30:800–802, 1945.
34. Morch-Lund, E.: Determination of bacterial resistance to penicillin sulfathiazole and streptomycin, Acta Pathol Microbiol Scand 26:821–839, 1949.
35. Bondi, A., Jr., Spaulding, E. H., Smith, F. E., and Dietz, C. C.: A routine method for the rapid determination of susceptibility to penicillin and other antibiotics, Am J Med Sci 213:221–225, 1947.
36. Howe, C. R.: Studies on the susceptibility of bacteria to various antibacterial agents with a comparison of the serial tube dilution and filter paper disc methods of testing, Surg Gynol Obst 91:669–672, 1950.
37. Lewin, W. and Rand, H.: Microbic sensitivity: A rapid technique for a wide range of sensitivity tests, S African Med Journal 40:34–35, 1966.
38. Welch, H.: Antibiotic sensitivity testings: Antibiotic Chemotherapy 5:321–323, 1956.
39. Jackson, G. G. and Finland, M.: Comparison of methods for determining sensitivity of bacteria to antibiotics in vitro, Arch Int Med 88:446–460, 1951.
40. Hoethe, I. and Struyk, A. P.: A modified method for evaluation of clinical usefulness of antibiotics, J Lab Clin Med 51:638–653, 1958.
41. Anderson, T. G. and Troyanosky, A.: Antibiotic susceptibility testing by the disc method, Antibiotic Annual 1959–1960:587–595, 1960.
42. Bauer, A. W., Perry, J. M. and Kirby, W. M. M.: Single disc antibiotic sensitivity testing of staphylococci, Arch. Int. Med., 104:208–216, 1959.
43. Bauer, A. W., Roberts, E. C. and Kirby, W. M. M.: Single disc versus multiple disc and plate dilution techniques for antibiotic sensitivity testing, Antibiotic Annual, 1959–1960: 574–580, 1960.
44. Bauer, A. W., Kirby, W. M. M., Sherris, J. C., and Turck, M.: Antibiotic susceptibility testing by a standardized single disc method, Am J Clin Path 45:493–496, 1966.
45. Rose, B. S. and Snyder, B.: "All or none" antibacterial discs tests in synthetic medium, Am J Clin Path 56:667–675, 1971.
46. Cheatle, E. L.: The single disc sensitivity test using, a zone size chart, Am J Clin Path 48:603–604, 1967.
47. Oberhoper, T. R. and Maddox, L.: Evaluation of a zone size chart for antibiotic susceptibility tests by disc diffusion, Am J Clin Path 54:596–601, 1970.
48. McGhie, D. and Finch, R.: Simple zone reader, for recording antibiotic deic zones, J of Clin Path 28:513–514, 1975.
49. Barry, A. L., Garcia, F., and Thrupp, L. D.: An improved single-disc method for testing the antibiotic susceptibility of rapidly-gorwing pathogens, Am J Clin Path 53:149–158, 1970.
50. Ericsson, H. and Sherris, J. C.: Antibiotic sensitivity testing; Report of an international collahorative study, Acta Path microbial Scand 217 (suppl.):1–90, 1971.
51. Garrod, L. P. and Waterworth, P. M.: Tests of bacterial sensitivity to drugs, Disease a Month:1–48, 1971.
52. Waterworth, P. M.: The disc sensitivity test, Medical Tech Lab 28:385–393, 1971.
53. Williams, R. F. and Bambury, J. M.: Mechanical rotary device for plating out bacteria on solid medium, J Clin Path 21:784–786, 1968.
54. Stokes, E. J.: Clinical bacteriology, Edward Arnold 3rd ed. 1968, London, p. 179.
55. Pearson, C. J. and Whitehead, J. E. M.: Antihiotic sensitivity testing: A modification of the Stokes method using a rotary plater, J Cin Path 27:430–431, 1974.

56. Blazevic, D. J., Koepcke, M H., and Matsen, J. M.: Quality control testing with the disc antibiotic susceptibility test of Bauer-Kirby, Sherris, Turck, Am J Clin Path 57:592–597, 1972.

57. Performance standards for antimicrobial disc susceptibility tests, as used in clinical laboratories: Tentative standards recommended by NCCLS subcommittee on antimicrobial susceptibility testing: Current techniques for antibiotic susceptibility testing, Charles C Thomas, Inc. Springfield, Ill. 1974.

58. Pital, A., Disque, D. T.,and Leise, J. M.: A new rapid plate method for determining antibiotic sensitivity, Antibiotic Chemotherapy 6:351–359, 1956.

59. Melia, J. L., Cook, E. L., and White, S. R.: Rapid antibiotic sensitivity testing utilizing zone size methodology, Am J Clin Path 56:59–63, 1971.

60. Jackson, J. L. W., Dye, W. F., and Mitchell, R. B.: Use of hemoglobin indicator for rapid method of determining antibiotic sensitivity of microorganisms, Texas Rep Biol Med 12:171–172, 1954.

61. Bass, J. A., Engley, F. B., Mitchell, R. B., et al: Evaluation of a rapid method (hemoglobin reduction) for determining antibiotic susceptibility of microorganisms; II: modifications in techniques, Antibiot Chemother 7:160–171, 1957.

62. Boyle, V. J., Faucher, M. E.,and Rose, P. R. W.: Rapid modified Kirby-Bauer susceptibility test with single high concentration antimicrobial discs, Antimicrob Ag Chemoth 3:418–424, 1973.

63. Petralli, J., Russell, E., Kataska, A., and Merigan, T. C.: On line computer quality control of antibiotic-sensitivity testing, N E J M 283:735–738, 1970.

64. Moellering, R. C., Mercier, B. A., Kunz, L. J., and Poitras, J. W.: Evaluation of a computer associated electronic zone analyzer in single disc antimicrobial susceptibility testing, Antimicrobial Ag Chemoth 2:95–102, 1972.

65. Schmith, K. and Reymann, F. E.: Clinical and experimental studies on the sensitivity of gonococci to sulfapyridine, Nordisk Medicine 8:2493–2499, 1940.

66. Sjostedt, S., Vahlne, G., and Berg, N.: The significance of chemoresistance determinations in the treatment of pneumonia with sulphonamide preparations, Nordisk Medicine 14:1696, 1780, 1942.

67. Sjostedt, S., Vahlne, G., and Berg, N.: Studies in pneumococcal immunity III: Determination of the resistance of the Pneumococci to sulphapyridine, Acta Pathol et Microbiol Scand 19:405–422, 1942.

68. Harper, G. J. and Cawston, W. C.: The in vitro determination of the sulphonamide sensitivity of bacteria, J Path Bact 57:59–66, 1945.

69. West, M. G., Doll, E. R., and Edwards, P. R.: Inhibition of salmonella cultures by streptomycin, Proc Soc Exp Biol 60:363–364, 1945.

70. Alexander, H. E. and Leidy, G.: Influence of streptomycin on type B. H. Influenzae, Science 104:101–102, 1946.

71. Frisk, A. R.: Use and dosage of antibiotics, Nordisk Medicine 43:323, 1950.

72. Frank, P. F., Wilcox, C., and Finland, M.: In vitro sensitivity of coliform bacilli to seven antibiotics, J Lab Clin Med 35:188–204, 1950.

73. Steers, E., Foltz, E. L., and Graves, B. S.: An inocula replicating apparatus for routine testing of bacterial susceptibility to antibiotics, Antibiotics Chemother 9:307–311, 1959.

74. Lederberg, J. and Lederberg, E. M.: Replica plating and indirect selection of bacterial mutants, J Bact 63:399–406, 1952.

75. Foltz, E. L., Steers, E., Graves, B. S., and Suriano, H. J.: Initial comparative study of susceptibility tests as performed with a replicating device, Antibiotics Annual 1959–1960:596–603, 1960.

76. Steers, E., Foltz, E. L., Graves, B. S., and Suriano, H. J.: Comparison of bacterial susceptibility to antibiotics as determined by the plate dilution method and by the disc method, Antibiotics Annual 1959–1960:604–613, 1960.

77. Mahony, D. E. and Chadwick, P.: A rapid method for measuring antibiotic sensitivity of bacteria, Canad J microbial 11:829–836, 1965.

78. Rammelkamp, C. H., Maxon, T.: Resistance of staphylococcus aureus to the action of penicillin, Proc Soc Exp Biol Med 51:386–389, 1942.
79. Spink, W. W., Ferris, V. and Vivino, J.: Comparative in vitro resistance of staph to penicillin and sodium sulfathiazole, Proc. Soc. Exp. Biol. 55:207–210, 1944.
80. Blair, J, E., Carr, M. and Buchman, J.: The action of penicillin on staphylococci, J. Immunol 52:281–292, 1946.
81. Peterdorf, R. G., Bennett, I. L., Jr., and Rose, M. C.: The sensitivity of pathogenic bacteria to a series of antibiotics, Johns Hopkins Hosp Bull 100:1–13, 1957.
82. Carroll, G., Allen, H. N., and Doubly, E. K.: Study of bacillary, infection of urinary tract, J A M A 135:683–686, 1947.
83. Pulaski, E. J. and Sprinz, H.: Streptomycin in surgical infections I: Laboratory studies, Ann Surg 125:194–202, 1947.
84. Schneierson, S. S. and Amsterdam, S.: A simplified tube procedure for the routine determination of bacterial sensitivity to antibiotics, Am J Clin Path 31:81–86, 1959.
85. Schwarz, L. H. and Brown, B. A.: An improved rapid method of tube dilution antibiotic sensitivity testing, Antibiotics Chemotherapy 4:333–337, 1954.
86. Schneierson, S. S.: A simple rapid disc-tube method for determination of bacterial sensitivity to antibiotics, Antibiotics Chemoth 4:125–132, 1954.
87. Isenberg, H. D., Reichler, A., and Wiseman, D.: Prototype of a fully automated device for determination of bacterial antibiotic susceptibility in the clinical laboratory, Appl microbiol 22:980–986, 1971.
88. Thornsberry, C., Baker,C. N., and Kirven, L. A.: Evaluation of an automated method for antimicrobial susceptibility testing, Adv automated Anal 4:99–102, 1973
89. Praglin, J., Curtiss, A., Longhenry, D., and McKie, J.: Autobac I: A 3 hour automated antimicrobial susceptibility system. I: system description p. 197–208. In C. Henden and T. Illeni (ed), Automation in microbiology and Immunology, John Wiley and Sons, Inc., New York, 1974.
90. Thornsberry, C., Gavan, T. L., Sherris, J. C., Balows, A., Matsen, J. M., Sabath, L. D., Schoenknecht, F., Trupp, L. D., and Washington, J. A.: Laboratory Evaluation of a rapid automated susceptibility testing system: Report of a collaborative study, Antimicrob Ag Chemoth 7:466–480, 1975.
91. Harrington, B. J., Hanson, D. J.: A clinical evaluation of a three-hour automated antimicrobial susceptibility system, Laboratory medicine 6:40–44, 1975.
92. McGowan, J. E., Ayres, C., and Sabath, L. D.: Rapid semiquantitative testing of antibiotic susceptibility: Ue of a multicell disc, elution system, Antimicrob Ag Chemother 7:543–548, 1975.
93. Sellers, W., Schmidt, P., and Ball, R.: Rapid antibiotic sensitivity test, IIndustrial medicine, 38:50–52, 1969.
94. Berkman, R. M., Wyatt, P. J., and Phillips, D. T.: Rapid detection of penicillin sensitivity in *Staph. aureus*, Nature 228:458–460, 1970.
95. Koch, W. and Kaplan, D: Micromethod for measuring microbial sensitivity to drugs, Nature 208:50–51, 1965.
96. Marymount, J. H., Jr. and Wentz, R. M.: Serial dilution antibiotic sensitivity testing with the microtitration system, Am J Clin Path 45:548–551, 1966.
97. Sever, J. L.: Application of a microtechnique to viral serological investigations, J Immunol 88:320–329, 1962.
98. Takatsy, G.: The use of spiral loops, in serological and virological micromethods, Acta Microbiol Hung 3:191, 1956.
99. Harwick, H. J., Weiss, P., and Fekety, Jr., R. F.: Application of microtitration techniques to bacteriostatic and bactericidal antibiotic susceptibility testing, J Lab Clin Med 72:511–516, 1968.
100. Chitwood, L. A.: Tube dilution antimicrobial susceptibility testing: Efficacy of a microtechnique applicable to diagnostic laboratories, Appl Microbiol 17:707–709, 1969.
101. Gavan, T. L. and Town, M. A.: A microdilution method for antibiotic susceptibility testing,

Am J Clin Path 53:880–885, 1970.

102. MacLowry, J. D. and Marsh, H. H.: Semiautomatic microtechnique for serial dilution antibiotic sensitivity testing in the clinical laboratory, J Lab Clin Med 72:685–687, 1968.

103. MacLowry, J. D., Jaqua, M. J., and Selepak, S. T.: Detailed methodology and implementation of a semiautomated serial dilution microtechnique for antimicrobial susceptibility testing, Appl Microbiol 20:46–53, 1970.

104. Gavan, T. L. and Butler, D. A.: Automated microdilution antimicrobial susceptibility testing, Bacteriol Proc 71:115, 1971.

105. Gerlach, E. H.: Microdilution I: A comparative study. Current technique for antimicrobial susceptibility testing, Charles C Thomas, Inc., Springfield, Illinois, 1974.

106. Gavan, T. L. and Butler, D. A.: An automated microdilution method for antimicrobial susceptibility testing. Current technique for antimicrobial susceptibility testing, Charles C Thomas, Inc., Springfield, Illinois, 1974.

107. Goss, W. A. and Cimijotti, E. B.: Evaluation of an automatic diluting device for microbiological application, Appl Microbiol 16:1411–1416, 1968.

108. Tippet, L. O., Zelenick, L. D., and Robb, C. A.: Modification of the microtiter technique for antimicrobial drug susceptibility testing by incorporation of indicators, Appl Microbiol 20:342–345,1970.

109. Rolinson, G. N., Russell, E. J.: A new method for antibiotic sensitivity testing, Lancet II:745–746, 1971.

110. Rolinson, G. N. and Russell, E. J.: New method for antibiotic susceptibility testing, Antimicrob Ag Chemother 2:51–56, 1972.

111. Binford, J. S., Binford, L. F., and Adler, P.: A semi-automated microcalorimetric method of antibiotic sensitivity testing, Am J Clin Path 59:86–94, 1973.

112. Hein, A. H., Curtin, J. A., and Levin, G. V.: Determination of antimicrobial activity by a radioisotope method, Antimicrob Ag Chemother: Proceedings of the conference on antimicrobial agents, Washington 1960:123–128, 1960.

113. Moser, S. A., and Pollack, J. D.: A rapid sensitive radiospirometric technique to assay the antibiotic sensitivity of slow-growing microorganisms. Proceedings of the 15th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, September 23–26, 1975.

114. Dorfman, W. A., Moldavskaya, E. A., Kastorskaya, T. L., and Zasyskina, P. A. (1946) Amer Rev Soviet Med 3:500, cited in ref. 115.

115. Heatley, N. G.: The assay of antibiotics: Antibiotics, Florey, H. W., Chain, E., Heatley, N. G., Jennings, M. A., Sanders, A. G., Abraham, E. B., and Loo, M E., eds., Vol. 1, Oxford University Press, London, 1949, p. 110–199.

116. Sabath, L. D.: The assay of antimicrobial compounds, Human Path 7:287–295, 1976.

The Mount Sinai Journal of Medicine
Vol. 44, No. 1, January-February, 1977
Printed in U.S.A.

Clinical Pharmacology in Infectious Diseases

BURT R. MEYERS, M.D. AND SHALOM Z. HIRSCHMAN, M.D.

The clinical discovery of penicillin in 1940 and the subsequent burgeoning development of other effective antimicrobial agents have only taken place in the past 35 years. Techniques for the in vitro testing of antibiotics quickly were developed and have become the cornerstone of screening and laboratory testing of these agents. However, no clear-cut evidence has as yet been produced to allow definite correlation between results of laboratory sensitivity tests and therapeutic efficacy, including limiting toxicity, in the infected patient.

It became necessary to study the pharmacokinetics of antimicrobial agents to determine if at least in the normal human volunteer the particular drugs could be found in body compartments such as serum, urine and cerebrospinal fluid (CSF). An antibiotic with enormous antimicrobial activity in vitro will be of no clinical value if it cannot reach the infected area. Fortunately, marked strides have been made in the study of the pharmacokinetics of antimicrobial agents allowing more effective clinical usage of the antibacterial activities of these drugs.

Clinical Pharmacology

In order to enable quantitation and comparison of the antimicrobial efficacy of the drugs, parameters such as the minimal inhibitory (MIC) and bactericidal concentrations (MBC) and inoculum size were introduced. It readily became apparent that variations in inoculum size could change the measured MIC and MBC (1). Furthermore. use of different media (2), and varying the pH or cationic concentration of media also could affect the activity of certain agents (3, 4). Yet, despite these problems the pharmaceutical industry developed compounds that could achieve levels in body fluids that were equal to or greater than the MIC of most pathogenic bacteria. It is not yet determined what serum levels of an antibiotic relative to the MIC are required for therapeutic efficacy. Also unknown is the time necessary for the agent to come in contact with the offending pathogen. Prevailing opinions suggest that the greatest possible multiple of MIC or MBC be achieved in serum for the greatest length of time.

However, in final analysis, even when armed with the most sophisticated pharmacokinetic data on an antibiotic, it is the clinical efficacy of the compound that finally must be shown. In this regard, the host with or without

From the Division of Infectious Diseases, Department of Medicine, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Dr. Shalom Z. Hirschman, Mount Sinai School of Medicine, Fifth Avenue and 100 Street, New York, N. Y. 10029.

an underlying disease, together with any potent immunostatic and cytotoxic agents administered, must *interact* with the offending microbial pathogen and antibiotic. The successful resolution of this battle determines the therapeutic efficacy of an antimicrobial agent.

Compartmental Analysis

Early thinking on pharmacokinetic analysis in humans assumed that all drugs were instantly distributed equally throughout all the extracellular fluids and body tissues which could be considered as a single compartment (5). Based on this assumption, certain pharmacokinetic concepts were suggested. The half-life of a drug ($T_{½}$), the time it takes for ½ the amount of drug to be eliminated, was a function of the slope of the curve when concentration of drug was plotted against time on semi-long paper. The apparent volume of distribution (AVD), assuming a one compartmental system and instantaneous distribution, could be easily calculated and was equal to the administered dose divided by the serum concentration in the steady state. This volume represents the distribution of a drug throughout all the tissues of the body. It is a hypothetical space that may approximate the extracellular fluid volume, may be greater than the total fluid volume of body, and may in certain circumstances, such as uremia, contract in size. The greater the AVD, the lower the serum concentration for the same $T_{½}$.

Thus in the steady state at a constant rate of infusion

$$\text{Rate of Infusion (mg/hr)} = C \times V \times K$$

where C, is plasma concentration (μg/ml); V, is AVD (liters); and K, is the rate constant of elimination (hr^{-1}). The value of K may be calculated from the half-life

$$K = \frac{0.693}{\mathrm{T}_{½}}$$

Following an intramuscular dose of drug AVD may be calculated from

$$\text{AVD} = \frac{\mathrm{I}}{C_0}$$

where I, is the dose administered and C_O is the serum concentration extrapolated to zero time.

However, this model did not take into consideration the actual distribution of drugs in man (6). The concentrations of compounds in different body spaces and their time of occurrence could not be described by the one compartment system. It readily became apparent that there were two compartments into which drugs were distributed (7). This two compartment system assumes that there is a small central and a larger peripheral compartment. The central compartment consists of the blood, and extracellular spaces of highly perfused organs such as lungs, liver, heart and kidney. Administered drugs are thought to distribute rapidly throughout this compartment and equilibrium is reached between blood and tissue spaces. The second compartment consists of organs less well perfused such as muscle, fat and skin which the drugs enter more slowly.

This model assumes that drugs enter and are eliminated only from the central compartment. There is however a reversible transfer between the central and peripheral compartments; thus the latter serves a reservoir function. Another assumption is that "first order kinetics" explain the movement of drugs between compartments. Thus, the rate of removal of a drug from a compartment is proportional to its concentration. Based on the above assumptions, formulae describing first order constants associated with movements of compounds in and out of each compartment can be calculated. The elimination rate constant which reflects the sum of all routes of drug exit from the central compartment, and drug concentration can be calculated. The total apparent volume of distribution in this system is really two volumes, that of central and peripheral compartments. The distribution between these volumes reflects blood flow, and other factors which may include molecular size, electrical charge, protein binding and possibly inflammatory changes (8).

Calculations are based on the assumption that instantaneous distribution in the central compartment occurs after rapid administration of the drug at which time concentration in the peripheral compartment is zero (7). Plotting the log concentration versus time, a curve with two components is obtained. The first component, called the alpha or distribution phase, represents the rapid distribution from central to peripheral compartments; a $T_{1/2}$ for this phase can be calculated. Following this distribution, the curve enters the slower, beta, or elimination phase, representing the disappearance of drug (irreversible elimination) from the central compartment. The $T_{1/2}$ for this beta phase can be calculated, and represents the most important pharmacokinetic parameter of the drug. The total apparent volume of distribution is the sum of the volume of the central and peripheral compartments. AVD can be determined two ways, one following single intravenous dosing, and the other following continuous intravenous infusion of a drug at the same rate. The latter method assumes no net transfer between compartments.

The clearance of a drug represents the elimination of the drug from the central compartment, and depends only upon a first order elimination rate constant. This parameter is related to routes of drug removal including urinary, fecal and respiratory excretion, as well as bio-transformation. The drug clearances are related to $T_{1/2}$ and AVD. The renal clearance of a drug easily can be calculated by dividing the rate of urinary excretion by the serum concentration.

$$\text{Clearance} = \frac{\text{Urinary excretion (mg/min)}}{\text{Serum concentration (mg/ml)}}$$

Some of the topics presented above have recently been discussed in detail (7).

It appears necessary in order to cure bacteremia to achieve serum levels of antibiotic equal at least to the MIC of the drug for the offending pathogen. However, it is apparent that most infections take place in organs and tissue spaces. Thus, it is necessary to consider the mechanisms whereby antibiotics enter these spaces. In serum antibiotics exist in equilibrium between the free state and bound to serum proteins. Examination of antibiotic concentrations in tissue spaces reveal that only free drug is present (9, 10).

Thus, it is *free* drug in either cerebrospinal, synovial, pleural, pericardial, or peritoneal fluid that interacts with bacteria. A recent study of concentrations of certain antibiotics in bronchial secretions revealed that multiple factors including molecular size, electrical charge, lipid solubility and, probably most important, degree of inflammation account for the observed drug concentrations (8). It is important to note that enzymes such as beta lactamases that can inactivate penicillins or cephalosporins may be present in abscesses; high cationic concentrations may inhibit the activity of aminoglycoside antibiotics (3, 4). A recent report described the reversible binding of large concentrations of gentamicin to pus (11) rendering the compound inactive. This mechanism may account for the coexistence in abscesses of large concentrations of antibiotics with viable sensitive bacteria (12).

Experimental studies of antibiotic concentrations in subcutaneously implanted clots, again show that free drug is important (13). It therefore is important to be aware of the relative protein binding of antibiotics though values may differ depending on the method of testing employed (13). Pharmacologic studies have shown that rapid administration by IV bolus injection will achieve much higher peak serum levels than constant infusion of a drug (14). Other studies have shown that intermittent perfusion will lead to higher tissue or clot levels than constant infusion (14). Since transfer between central and peripheral compartments is based on first order kinetics and is proportional to the serum concentration we employ the intravenous bolus method to achieve higher serum concentration with either the penicillin or cephalosporin antibiotics, in the hope of achieving higher tissue levels. This method of therapy seems especially suited for treatment of infective endocarditis and bacterial meningitis; although treatment with this bolus method seems more logical, data proving increased efficacy have not appeared.

Certain body compartments, such as the cerebrospinal fluid (CSF), prostate and eye deserve special consideration. Penetration of antibiotics into CSF depends upon factors such as diffusion; active transport systems may play a role in the bi-directional movement of penicillin (15). Probenecid may interfere with these transport systems and increase CSF penicillin levels. Diffusion of other antibiotics into CSF appears to be a function of molecular size, lipid solubility, ionization and protein binding. Sulfonamides, isoniazid and chloramphenicol may reach CSF levels of 40 to 50% of the serum level in the presence of normal meninges (16). A major factor determining CSF penetration is the degree of inflammation of meningeal membranes. Whereas the penicillins penetrate the normal meninges very poorly, the presence of inflammation increases the penetration (15, 17). Studies on the concentration of penicillin G in CSF when probenecid has been administered have been carried out. It appears that probenecid has a three-fold effect (15). First, it raises the serum level by inhibiting the renal and biliary excretions of penicillin G. Secondly, probenecid competes for penicillin binding sites of serum protein and hence the diffusable fraction of penicillin is increased. Finally, the transport system postulated for the removal of penicillin from the cerebrospinal fluid is inhibited by probenecid. However, it also appears that probenecid competes with penicillin for entry into the brain as it competes for binding serum protein. Fishman (15) concluded that, though serum levels of penicillin were raised, brain levels were decreased and therefore probenecid should not be given along with penicillin in the treatment of infections of the central nervous system (15). Aminoglycoside antibiotics do not penetrate CSF well even in the presence of inflammation; intrathecal administration may be necessary for treatment (16, 18). Penetration of the cephalosporins into CSF is poor under most circumstances. When cephalothin is employed the less active des-acetyl derivative (19) competes at an entry site with the parent compound; the reason for poor penetration by other cephalosporin compounds is not apparent.

The penetration of antimicrobial agents into the human eye has been less well studied (20). Experimental studies using the inflamed rabbit eye (21) show that compounds that are not highly bound to protein are able to penetrate into the aqueous and the vitreous humors; antibiotics such as penicillin, ampicillin, methicillin (22), cephaloridine (23), lincomycin (24), isoniazid (25) and chloramphenicol (26) penetrate well; oxacillin (27) and cefazolin are both very highly bound to protein and penetrate poorly.

Penetration of antibiotics into the human prostrate is rather poor. Presently available data were derived mainly from the dog (28). These studies have shown that the pH within the prostate is 6.4 or less. Thus, given the pK of most antimicrobial agents, it appears they will be present in the ionized form. Agents like erythromycin may penetrate the prostatic epithelium, but at the prostatic pH will be less active. Recent work suggests that trimethoprim (but not sulfamethoxazole) may penetrate into prostatic secretions (29); clinical studies with trimethoprim in combination with sulfonamides may prove rewarding.

Treatment of chronic bacterial prostatis remains difficult at best. This problem has been studied in dog models to determine the diffusion of antimicrobial agents from the plasma into prostatic fluid. Except for basic macrolides erythromycin and oleandomycin, none of the antimicrobial drugs tested could be detected in the prostatic fluid, even when the serum concentrations were very high (28). It should be noted that the levels of erythromycin in prostatic fluid were several times the simultaneous plasma level. The explanation for this is that the prostatic fluid is distinctly acid with a pH of 6.4 compared to a plasma pH of 7.4. It is known that almost all antimicrobial agents are either weak acids or weak bases. With a lipid membrane it is necesssary for the drug to be lipid soluble to traverse and if the drug is charged or in the ionized form, it is essentially lipid insoluble. Thus, an antimicrobial drug which is lipid insoluble is limited to distribution throughout the extracellular fluid. Antibiotics such as penicillin, ampicillin and cephalosporins are lipid insoluble and are also acids with a pK in the range of 2–3. At a plasma pH of 7.4, they are in the charged form, which precludes their entering the prostatic fluid.

Another peripheral vascular space may be represented by human bone. There is a paucity of studies dealing with the penetration of antimicrobial agents into bone. Norden (30) has pointed out that antibiotics may penetrate infected bone in a rabbit model of osteomyelitis. Some data have been presented on levels of antimicrobial agents in non-infected human bone (31, 32).

Most antibiotics used in the treatment of urinary tract infection are excreted into urine; with many, the levels found are markedly higher than those in serum and in some cases, as with cephalexin, concentrations exceeding 10,000 μg/ml are common (1). For years, the necessity to achieve higher serum or urine levels to cure bacteriuria or even pyelonephritis was debated. It was suggested that achieving high urinary levels was more important than high serum levels, but in many cases the data were not statistically significant (33–35). Clinical experience showing the effectiveness of nitrofurantoin derivatives, drugs that achieve almost no serum levels but very high urine levels, seemed to bear out this suggestion. However, compounds such as chloramphenicol that achieve high serum levels but low urine levels, have also been effective in the treatment of urinary tract infection. We have on occasion employed this drug with success in the special patient with renal failure, whose renal function has deteriorated reversibly due to infection.

Many compounds, such as penicillins, cephalosporins, nitrofurantoins and aminoglycosides cannot be found in urine of patients with marked renal impairment and diminished creatinine clearance (34). Cefazolin (35), and cephalexin (37) have been found in the urine of such patients. Aminoglycosides should be given with extreme caution to such patients for not only may no clinical response be seen, but the chance for increased toxicity is apparent. The nitrofurantoins will not get into urine in such patients, and toxicity is markedly increased in renal failure (38).

The pharmacokinetics of antibiotics in the biliary tract has been studied (39–41). Whereas most authors agree that in the presence of duct obstruction no antibiotics will be found proximal to the obstruction, the data in the absence of obstruction seem to vary. Recent studies have shown that both cephalothin (42, 43) and gentamicin (40, 41) achieve biliary levels that are only a small fraction of those in the serum, and in many cases only a negligible level of the antibiotic was found; cefazolin, however, achieved high levels in the biliary tree (42, 44). On the other hand, both cephalothin and gentamicin have been used successfully in the treatment of infections of the biliary tract. It may be that if biliary samples had been taken earlier adequate levels would have been found; since the required length of time of contact between bacteria and drug is unknown, it may be that short-lived levels are sufficient for therapeutic efficacy. Experimentally, staphylococci are markedly changed in the presence of penicillin for only 20 min. (45).

Another example of the need for knowing the pharmacokinetics of an antibiotic may be appreciated in regard to prophylaxis of meningococcal infections. Although penicillin and other agents are efficacious in the therapy of established infections, they are not protective as prophylactic agents (46). It has been suggested that mucosal or pharyngeal levels are inadequate to inhibit growth of meningococci.

Knowledge of the absorption of antimicrobial agents from surfaces such as synovium, denuded wounds, or the peritoneal cavity is extremely important. First, data on the efficacy of topically applied antibiotics are sorely lacking. In some studies in which agents were used in irrigation devices for treatment of osteomyelitis, the patients were treated systemically as well (47, 48). Of more importance is the fact that some agents may be absorbed in large amounts and toxicity follows. Ototoxicity after topical neomycin and other aminoglycosides has been reported (49, 50). In many instances synovitis related to the local toxicity of antibiotic on the synovial membrane has occurred. Another problem seen with topical administration of antibiotics may be superinfection with a more resistant microorganism; whereas the initial cultures may have grown a staphlococcus, Pseudomonas or Serratia sp. may later be found in effluent irrigating tubes.

Though never proved to be efficacious, many physicians still add antibiotics to the dialysis solutions employed in peritoneal dialysis (51). Earlier studies showed that antibiotics crossed the peritoneal membrane and blood levels were obtained (52). In some cases an equilibrium between serum and peritoneal fluid occurred (ampicillin), but with tetracycline the level in patient's serum kept increasing proportionally to the number of dialyses; the potential for the "uremic" syndrome with this compound is obvious. Aminoglycoside antibiotics placed in the peritoneum have caused apnea.

Many physicians employ antibiotics prophylactically in patients with valvular heart disease undergoing dental work. The use of agents such as penicillin for three days prior to and after dental work seems unnecessary. It has been shown that prophylactic antibiotics cannot prevent bacteremia. The value of prophylactic agents is to achieve the highest blood level at the height of the bacteremia; thus, they should be given parenterally 1–2 hours prior to dental manipulation.

Probably the most important factor in determining the clinical pharmacology of antimicrobial agents is the host. Studies on oral absorption have usually been determined in normal volunteers, and not in the febrile or otherwise sick patient. A study of antibiotic absorption in the presence of certain gastrointestinal diseases revealed levels were substantially higher (53). Intramuscularly administered agents may be of no value in the hypotensive patient since they can not be delivered to the circulatory system. The patient's renal function must be constantly monitored especially when aminoglycoside antibiotics and penicillin or its derivatives are given; it is necessary to modify the dose of these agents and increase the interval of their administration when renal dysfunction is present. Certain formulae and nomograms have been published for use in patients with renal failure. However, recent papers, in which blood levels were measured, have suggested that these formulae are inaccurate in predicting the observed levels (54). Fever may decrease the serum level of gentamicin (55); the serum level of gentamicin is unevenly proportional to the hematocrit (56). In the case of aminoglycosides, toxicity of the compounds is related to serum levels. The toxic effects are on the 8th cranial nerve (57) and the renal tubules (58). As both peak and trough levels increase ototoxicity (57) and nephrotoxicity (59) appear to increase. Other factors correlating with increased toxicity of aminoglycosides include prior administration of aminoglycosides, advancing age, duration of therapy, dose, route of administration, serum levels and concomitant use of other ototoxic or nephrotoxic agents (54).

As therapeutic agents are used in an ever increasing number, it becomes necessary to study the interaction of these agents with antibiotics. It is not the scope of this paper to discuss the multiplicity of interactions that may occur among these agents for this has been recently reviewed (60). Mechanisms that have been studied include a displacement from protein carrier sites of antimicrobials by other compounds, as well as competition for renal tubular secretion and interaction between other drugs and antibiotics in relation to their metabolism by hepatic enzymes.

In many cases the host will have underlying disease which may in itself restrict the route of administration of the compound, such as thrombocytopenia, infiltrative bowel disease, ulcers or diarrhea. Often patients with neoplastic diseases or those with immunologic diseases are receiving cytostatic agents. We have not found any in vitro antagonism between cytosine arabinoside or methotrexate and cephalothin or clindamycin (unpublished data).

However, the admixture in the same bottle or soluset of penicillin or cephalosporins with aminoglycosides may lead to inactivation of the latter compounds (61). On the other hand, diuretics affecting the renal tubules may enhance the toxicity of the aminoglycosides and these should not be given simultaneously.

In summary, it is necessary for the physician to be cognizant of a multiplicity of facts in order to wisely and most accurately treat patients with infectious diseases. First, one must be aware of the spectrum of antimicrobial activity of the agent. Of equal importance is a knowledge of the pharmacokinetics of antimicrobial agents; this includes not only knowledge of absorption, serum levels and excretion, but whether the compound can transverse certain important membranes such as pleura, synovia or meninges. Finally, one must be aware of the toxic manifestations of antimicrobial agents, and factors which may potentiate these toxicities. All of the above must be integrated with the knowledge that infectious diseases can only be solved in a host functioning immunologically and able to marshal the white blood cell response necessary to combat infection.

The antibiotics available to the physician are potent adversaries of individual microorganisms but their misuse can further compromise the health of the patient. We must never forget the warning, Primum non nocere!

References

1. Meyers, B. R., Kaplan, K., and Weinstein, L.: The Microbiological and Pharmacological Behavior of Cephalexin, Clin Pharmacol Therap 10:810–816, 1969.
2. Meyers, B. R., and Hirschman, S. Z.: Tobramycin: In Vitro Antibacterial Activity of a New Aminoglycoside, J Clin Pharmacol 12:313–320, 1972.
3. Davis, S. D., and Iannetta, A.: Influence of Serum and Calcium on the Bactericidal Activity of Gentamicin and Carbenicillin on Pseudomonas aeruginosa, Appl Microbiol 23:775–779, 1972.
4. Davis, S. D., and Iannetta, A.: Antagonistic Effects of Calcium and Serum on the Activity of Tobramycin against Pseudomonas, Antimicrob Agents Chemother 1:466–469, 1972.
5. Gibaldi, M., Schwartz, M. A., and Plaut, M. E.: Serum Levels of Penicillins: a Pharmacokinetic View, Antimicrob Agents Chemother 1968:378–381, 1969.
6. Riegelman, S., Loo, J. C. K., and Rowland, M.: Shortcomings in Pharmacokinetic Analysis by Conceiving the Body to Exhibit Properties of a Single Compartment, J Pharm Sci 57:117–123, 1968.
7. Greenblatt, D. J., and Koch-Weser, J.: Clinical Pharmacokinetics, N Eng J Med 293:702–705, 964–970, 1975.
8. Wong, G. A., Pierce, T. H., Goldstein, E., and Holprich, P. D.: Penetration of Antimicrobial Agents into Bronchial Secretions, Amer J Med 59:219–223, 1975.
9. Kunin, C. M.: Drugs, Receptors and Serum Protein Binding, N Eng J Med 281:1188–1189, 1969.
10. Kunin, C. M.: Clinical Significance of Protein Binding of the Penicillins, Ann NY Acad Sci 235:282–290, 1974.
11. Bryant, R. E., and Hammond, D.: Interaction of Purulent Material with Antibiotics Used to Treat Pseudomonas Infections, Antimicrob Agents Chemother 6:702–707, 1974.
12. Black, P., Graybill, J. R., and Charache, P.: Penetration of Brain Abscess by Systemically Administered Antibiotics, J Neurosurg 38:705–709, 1973.
13. Barza, M., Brusch, J., Bergeron, M. G., and Weinstein, L.: Penetration of Antibiotics into Fibrin Loci In Vivo. III. Intermittent versus Continuous Infusion and the Effect of Probenecid, J Infect Dis 129:73–78, 1974.
14. Barza, M., and Weinstein, L.: Some Determinants of the Distribution of Penicillins and Cephalosporins in the Body. Practical and Theoretical Considerations, Ann NY Acad Sci 235:613–620, 1974.
15. Fishman, R. A.: Blood-Brain and CSF Barriers to Penicillin and Related Organic Acids, Arch Neurol 15, 113–124, 1966.
16. Rahal, J. J.: Treatment of Gram-Negative Bacillary Meningitis in Adults, Ann Intern Med 77:295–302, 1972.
17. Smith, H., Lerner, P. I., and Weinstein, L.: Neurotoxicity and Massive Intravenous Therapy with Penicillin, Arch Intern Med 120:47–53, 1967.
18. Rahal, J. J., Hyams, P. J., Simberkoff, M. S., Rubenstein, E.: Combined Intrathecal and Intramuscular Gentamicin for Gram-Negative Meningitis, N Eng J Med 290:1394–1398, 1974.
19. O'Callaghan, C. H., and Muggleton, P. W.: The Formation of Metabolites from Cephalosporin Compounds, Biochem J 89:304–308, 1963.
20. Barza, M., and Baum, J.: Penetration of Ocular Compartments by Penicillins. Analysis of Factors Affecting Intraocular Concentration and Half-Life, Survey Ophthal 18:71–82, 1973.
21. Leopold, I. H., and La Motte, W. O., Jr.: Penetration of Penicillin in Rabbit Eyes with Normal, Inflamed and Abraded Corneas, Arch Ophthalmol 33:43–46, 1945.

22. Records, R. E., and Ellis, P. P.: The Intraocular Penetration of Ampicillin, Methicillin and Oxacillin, Amer J Ophthalmol 64:135–143, 1967.
23. Records, R. E.: Intraocular Penetration of Cephaloridine, Arch Ophthalmol 81:331–335, 1969.
24. Becker, E. F.: The Intraocular Penetration of Lincomycin, Amer J Ophthalmol 67:963–965, 1969.
25. Knapp, P., and von Sallmann, L.: Treatment of Experimental Ocular Tuberculosis with Isoniazid, Amer J Ophthalmol 38:199–205, 1954.
26. Leopold, I. H., Nichols, A. C., and Bogel, A. W.: Penetration of Chloramphenicol (Chloromycetin) into the Eye, Arch Ophthalmol 44:22–36, 1950.
27. Records, R. E.: Human Intraocular Penetration of Sodium Oxacillin, Arch Ophth Ophthalmol 77:693–695, 1967.
28. Stamey, T. A., Meares, E. M., Winningham, D. J.: Chronic Bacterial Prostatitis and the Diffusion of Drugs into Prostatic Fluid, J Urol 103:187–194, 1970.
29. Stamey, T. A., Bushby, S. R. M., and Bragonje, J.: The Concentration of Trimethoprim in Prostatic Fluid: Non-ionic Diffusion or Active Transport, J Infect Dis 128S:686–690, 1973.
30. Norden, C. W.: Experimental Osteomyelitis. II. Therapeutic Trials and Measurements of Antibiotic Levels in Bone, J Infect Dis 124:565–571, 1971.
31. Kolczun, M. C., Nelson, C. L., McHeury, T. L., Gaven, P., and Pinovich, P.: Antibiotic Concentration in Human Bone, J Bone Joint Surg 56A:305–310, 1975.
32. Nicholas, P., Meyers, B. R., Levy, R. N., and Hirschman, S. Z.: Concentration of Clindamycin in Human Bone, Antimicrob Agents Chemother 8:220–221, 1975.
33. McCabe, W. R., and Jackson, G. G.: Treatment of Pyelonephitis: Bacterial Drug and Host Factors in Success or Failure Among 252 Patients, N Eng J Med 272:1037–1044, 1965.
34. Stamey, T. A., Govan, D. E., and Palmer, J. M.: Localization and Treatment of Urinary-Tract Infections: Role of Bactericidal Urine Levels as Opposed to Serum Levels, Medicine 44:1–36, 1965.
35. Stamey, T. A., Fair, W. R., Timothy, M. M., Millar, M. A., Mihars, G., and Lowery, Y. C.: Serum Versus Urinary Antimicrobial Concentrations in Cure of Urinary-Tract Infections, N Engl J Med 291:1159–1163, 1974.
36. Craig, W. A., Welling, P. G., Jackson, T. C., and Kunin, C. M.: Pharmacology of Cefazolin and Other Cephalosporins, J Infect Dis 128S:347–353, 1973.
37. Meyers, B. R.: Cephalexin: In Vitro Studies, Pharmacologic Parameters, and Clinical Usage, Clin Med 81:23–27, 1974.
38. Felts, J. H., Hayes, D. M., and Gergen, J. A.: Neural, Hematologic and Bacteriologic Effects of Nitrofurantoin in Renal Insufficiency, Amer J Med 51:331–339, 1971.
39. Mortimer, P. R., Mackie, D. B., and Haynes, S.: Ampicillin Levels in Human Bile in the Presence of Biliary Tract Disease, Brit Med J 2:88–89, 1969.
40. Mendelson, J., Portnoy, J., and Sigman, H.: Pharmacology of Gentamicin in the Biliary Tract of Humans, Antimicrob Agents Chemother 4:538–541, 1973.
41. Pitt, H. A., Roberts, R. B., Johnson, W. D.: Gentamicin Levels in the Human Biliary Tract, J Infect Dis 127:299–302, 1973.
42. Ratzan, K. R., Ruiz, C., and Irvin, G. L.: Biliary Excretion of Cefazolin, Cephalothin, and Cephaloridine in the Presence of Biliary Tract Disease, Antimicrob Agents Chemother 6:426–431, 1974.
43. Mendelson, J., Portnoy, J., Sigman, H., and Dick, V.: Pharmacology of Cephalothin in the Biliary Tract of Humans, Antimicrob Agents Chemother 6:659–665, 1974.
44. Brogard, J. M., Dorner, M., Pinget, M., Adloff, M., and Lavillaureix, J.: The Biliary Excretion of Cefazolin, J Infect Dis 131:625–633, 1975.
45. Pennington, J. H., and Grady, F. O.: Reversal of the Action of Penicillin, Nature 213:34–35, 1967.
46. Hoeprich, P. D.: Prediction of Antimeningococcic Chemoprophylactic Efficacy, J Infect Dis 123:125, 1971.
47. West, W. F., Kelly, P. J., and Martin, W. J.: Chronic Osteomyelitis: I. Factors Affecting the

Results of Treatment in 186 Patients, J Amer Med Assoc 213:1837–1842, 1970.

48. Kelly, P. J., Martin, W. J., and Coventry, M. D.: Chronic Osteomyelitis: II. Treatment with Closed Irrigation and Suction, J Amer Med Assoc 213:1843–1848, 1970.
49. Nachamie, B. A., Siffert, R. S., Bryer, M. S.: A Study of Neomycin Installation into Orthopedic Surgical Wounds, J Amer Med Assoc 204:687–689, 1968.
50. Kelly, D. R., Nilo, E. R., Berggren, R. B.: Deafness After Topical Neomycin in Wound Irrigation, N Engl J Med 280:1338–1339, 1969.
51. Axelrod, J., Meyers, B. R., Hirschman, S. Z., and Stein, R.: Prophylaxis with Cephalothin in Peritoneal Dialysis, Arch Intern Med 132:368–371, 1973.
52. Bulger, R. J., Bennett, J. V., and Boen, M. T.: Intraperitoneal administration of broad-spectrum antibiotics in patients with renal failure, J Amer Med Assoc 194:140–144, 1965.
53. Parsons, R. L., Hossack, G., and Paddock, G.: The Absorption of Antibiotics in Patients with Adult Celiac Disease, J Antimicrob Chemother 1:39–50, 1975.
54. Barza, M., Brown, R. B., Shen, D., Gibaldi, M., and Weinstein, L.: Predictability of Blood Levels of Gentamicin in Man, J Infect Dis 132:165–173, 1975.
55. Pennington, J. E., Dale, D. C., Reynolds, H. Y., and MacLowry, J. D.: Gentamicin Sulfate Pharmacokinetics: Lower Levels of Gentamicin in Blood During Fever, J Infect Dis 132:270–275, 1975.
56. Riff, L., and Jackson, G. G.: Pharmacology of Gentamicin in Man, J Infect Dis 124S:98–105, 1971.
57. Jackson, G. G., and Arcieri, G.: Ototoxicity of Gentamicin in Man: A Survey and Controlled Analysis of Clinical Experience in the United States, J Infect Dis 124S:130–137, 1971.
58. Wilfert, J., Burke, I., Bloomer, H. A., and Smith, C.: Renal Insufficiency Associated with Gentamicin Therapy, J Infect Dis 124S:148–155, 1971.
59. Dahlgren, J. G., Anderson, E. T., Hewitt, W. L.: Gentamicin Blood Levels: A Guide to Nephrotoxicity, Antimicrob Agents Chemother 8:58–62, 1975.
60. Kabins, S. A.: Interactions Among Antibiotics and Other Drugs, J Amer Med Assoc 219:206–212, 1972.
61. McLaughlin, J. E., and Reeves, D. S.: Clinical and Laboratory Evidence for Inactivation of Gentamicin by Carbenicillin, Lancet 1:261–264, 1971.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 1, January–February, 1977
Printed in U.S.A.

Colonization, Suprainfection and Superinfection: Major Microbiologic and Clinical Problems

LOUIS WEINSTEIN, PH.D., M.D. AND RICHARD B. BROWN, M.D.

Secondary bacterial infections have long been known to complicate untreated primary disease caused by viruses, bacteria and other organisms (1, 2), and, in some instances, to be responsible for death in otherwise relatively benign disorders. The introduction of effective antimicrobial agents, an approach that might have been predicted to decrease or even abolish this problem has, in fact, been associated with an increased risk of secondary invasion due to bacteria and fungi, many species of which have, in the past, been considered essentially "nonpathogenic." Although the development of medical and surgical knowledge and the application of new therapeutic modalities have prolonged the lives of patients with leukemia, hydrocephalus, chronic renal disease and a variety of immunosuppressed states, death has resulted from infection despite control of the basic disease (3–7).

Secondary bacterial invasion may be classified in 3 groups (8):

Colonization. de novo appearance of an increase in number of a previously present potential pathogen in the normal microflora, occurring spontaneously or after exposure to an antimicrobial agent;

Suprainfection. the development of microbiological and clinical evidence of secondary infection in a patient being treated with an antibiotic for a primary infectious disorder.

Superinfection. clinical and microbiological evidence of infection in a person not receiving antimicrobial agents, but related to the presence of an infectious or non-infectious disorder that increases susceptibility to infection.

The purpose of this paper is to review these phenomena briefly.

Colonization

Some areas of the body such as the skin, mouth, upper respiratory tract, gastrointestinal tract, urethra and vagina harbor an indigenous microflora. Exposure to therapeutic doses of all antibiotics produces moderate to profound alterations in the genera, species, and number of the members of the microbial population. Without exposure to drugs, the heterogenous populations that constitute the so-called normal flora tend to remain relatively stable for long periods of time. Multiple mechanisms are involved in establishing a system of checks and balances that maintains this stability. Among these are competition for food and space and the production of bacteriocins, acid, and other metabolic products as well as antibiotics. By eliminating bacteria sensitive to

From the Infectious Disease Division of the Peter Bent Brigham Hospital, and the Departments of Medicine of the Harvard Medical School, Boston, Ma. 02115.

Requests for reprints should be sent to: Dr. Louis Weinstein, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, Ma. 02115.

it, an antibiotic unstabilizes these mechanisms; this leads, in some instances, to overgrowth of one or more species to large numbers and they become the predominant organism (9, 10). Thus, treatment with penicillin G may result in establishment of H. influenzae in the upper respiratory tract of children, or coagulase-positive staphylococci may increase to large numbers in the intestinal tracts of patients receiving neomycin orally. Certain features of an antibiotic and its use play important roles in affecting such clinically important disruptions of the normal microflora. Among these are (a) the type of drug, (b) the dose employed, (c) the activity of the compound against various organisms and (d) the duration of hospitalization. Broad-spectrum agents or combinations of antibiotics exert greater effects than do those with more limited antimicrobial activity. Combined treatment with penicillin and tetracycline or penicillin plus streptomycin inhibits most Gram-positive bacteria and permits proliferation of coliforms and fungi. Drugs with narrow antibacterial spectra, including some semi-synthetic, penicillinase-resistant penicillins, alter the normal microflora less intensely so that some Gram-positive species persist; methicillin may be an exception. Large doses of penicillin G administered either orally or parenterally, increase the risk of colonization (11, 12). These produce a decrease in the numbers of pneumococci and some species of streptococci, have no effect on Neisseria and enterococci, and increase the number of coliform organisms, Pseudomonas and Serratia. Colonization by Enterobacter, Proteus morgani, Pseudomonas and Serratia has been reported to occur primarily in patients over 50 years of age. The length of stay in the hospital appears to increase the rate of colonization; 80% of individuals treated with antibiotics and hospitalized for longer than 10 days have been noted to become colonized (13). Persons with cardiac, neurological and neoplastic diseases seem to be more prone than others to be colonized by Gram-negative bacteria. The severity of the infection for which an antibiotic is given and the type of organism responsible for disease appear to be unrelated to the frequency of colonization (13).

In addition to changes induced in the *bacterial* ecology of patients, the administration of antibiotics may lead to profound changes in the *fungal* population. Not only do they do this by altering the numbers and types of bacteria so that the fungi normally present overgrow as a result of inhibition or abolition of the mechanisms that have controlled their numbers (see above), but some antimicrobial agents, especially the tetracyclines, actually stimulate the growth and increase the pathogenicity of some yeasts, particularly *Candida* (14, 15).

Although the above discussion has concentrated on colonization resulting from the exhibition of antimicrobial agents, it must be emphasized that changes in the indigenous microflora may occur in the absence of exposure to these drugs. There is evidence that untreated hospitalized patients acquire a variety of bacteria including coliforms and Pseudomonas on various areas of the skin; the source of these appears to be the patient's own intestinal tract. In addition, some organisms, primarily Pseudomonas, are acquired in hospitals by contact with respirators and other apparatus, or are spread from patients who carry them as members of the intestinal flora.

Suprainfection

Suprainfection is defined as a phenomenon in which microbiological and clinical evidence of a secondary infection appears during the course of therapy of a primary infectious process with an antibiotic. This results from changes in the normal microflora of the skin and the upper respiratory and gastrointestinal tracts induced by all antimicrobial agents given in therapeutic doses. Suppression or eradication of sensitive organisms results in overgrowth by resistant ones which now constitute the bulk of the flora. While this is an almost universal occurrence in treated patients, only some develop suprainfections. The factors involved in the pathogenesis of the superimposed infections are: a) *age*. children two years of age or less and adults over the age of 50; b) underlying acute or chronic pulmonary disease, but not tuberculosis; c) *duration of exposure to an antibiotic*. the incidence of suprainfection reaches its height after about 6 days of treatment and remains at about this level as long as drug is being administered; and d) *the breadth of spectrum of activity of the antibiotic*. the broader the range of action of the compound, the higher the risk of suprainfection (8, 13, 16, 17). The reason for the greater danger of broad-spectrum drugs is the degree to which they suppress multiple bacterial genera and species in a heterogeneous microbial population. Treatment with a narrow-spectrum agent such as penicillin causes much less disruption of the microbial ecology because it suppresses only a small number of genera and species. This results in minimal alterations in the relation of different organisms to each other, and does not create a situation in which a potential pathogen already present in the indigenous flora will overgrow, and produce infection. In contrast, exposure to a broad-spectrum antibiotic, especially if it is given orally, will suppress or eradicate a wide range of bacteria sensitive to the drug. This results in loss of the factors responsible for maintaining stability of the microflora and facilitates the rapid and extensive multiplication of drug-resistant, potentially pathogenic species that may reach an inoculum size large enough to invade and produce disease. An outstanding example of this phenomenon is staphylococcal enterocolitis developing in some individuals receiving chlortetracycline or neomycin, and is due to a particular bacteriophage type of the organism that is resistant to these antibiotics. That the risk of suprainfection is determined to a large extent by the range of antimicrobial activity of a drug is underscored by the frequency which this complication of therapy follows the use of specific agents. Thus, it has been noted (12, 16) that the incidence of suprainfections associated with administration of penicillin G is about 0.6%, with streptomycin 1.5%, with penicillin plus streptomycin 2.5% and with chlortetracycline about 20%.

Suprainfections may occur in the course of either therapy or prophylaxis with antibiotics. The lungs appear to be most often affected whether or not they are the site of primary infection for which chemotherapy was initiated. However, other areas may also be involved. Thus, it has been observed that patients treated with penicillin for a streptococcal pharyngitis may, after exhibiting a favorable response, develop a sore throat and fever during the course of therapy due to H. influenzae. Treatment of lower urinary tract infections with antibiotics may lead to suprainfection by bacteria resistant to the agent being given; a series of new infections associated with exposure to successive antibiotics have been observed in some patients with this disease. The prophylaxis of coma, stroke, viral infections such as influenza, poliomyelitis, varicella, measles and the common cold, and elective surgery and obstetrical and gynecological procedures has been complicated by suprainfection. The immunosuppressed individual appears to be highly susceptible to this complication when given an antibiotic for either prophylaxis or therapy; the organisms often responsible are opportunistic pathogens such as yeasts (Candida, Torulopsis glabrata), fungi (Aspergillus, Mucor), and bacteria (Pseudomonas, Herrellea, Serratia) that are resistant to most antimicrobial agents.

It should be emphasized that treatment with sulfonamides rarely, if ever, leads to the development of suprainfection. This is probably related to the relative lack of activity of these drugs against most members of the indigenous microflora, and little or no change in the interaction between bacteria. As a result, overgrowth of potential pathogens does not occur and suprainfection is prevented.

Differentiation between colonization and suprainfection is of critical clinical importance. The distinguishing feature is the presence of *active infection* associated with a change in the type of the predominating organism in the latter, and a mere alteration in the nature of the bacteria, even if one species becomes predominant, in the former. Colonization does not require change of the antimicrobial agent being given at the time a single organism becomes predominant. Although there are no supporting data, it has been suggested by some that the new organism be eradicated by treatment with an effective drug in order to reduce or eliminate the risk of superimposed infection. An approach that appears more reasonable is not to change therapy until there is clear-cut evidence of a superimposed suprainfection; if this is so, exhibition of an agent active against the predominant bacterial species is mandatory. The problems of both colonization and suprainfection demand continuous monitoring of the microbial population, particularly of the upper respiratory tract. As a single member of this population is reported by the microbiologist to be increasing to large numbers, the physician must be alert to the risk of suprainfection, and treat as soon as evidence for this appears, selecting the antimicrobial agent on the basis of the nature of the predominant colonizing organism. If unnecessary exposure to antibiotics is to be avoided, it must be recognized that colonization is a *microbiologic* and suprainfection a *clinical* phenomenon.

Superinfection

Infections Associated with Compromise of Cutaneous-Vascular Barriers. Medical management of many serious illnesses often involves the use of measures that compromise natural cutaneous defense mechanisms. Intravenous and intraarterial catheters and ventriculoatrial shunts provide ready pathways for the introduction of a variety of bacteria into the circulation. Although patients who require the use of such devices often have severe underlying disorders and are frequently given antimicrobial agents, the role of catheters and shunts alone in the pathogenesis of infections that eventuate is eminently clear.

Intravenous Catheters. Although intravenously placed polyethylene catheters have received wide attention as a primary causative factor in the pathogenesis of infections in recent years (7, 18, 19), it must be pointed out that, in many instances, they are only the final pathway for the introduction of microorganisms from a system that contains a variety of containers, many types of fluid and connecting tubes, any or all of which may be colonized by potentially pathogenic bacteria, yeasts and fungi. More than 25% of such catheters have been found to harbor organisms (20, 21), and their use has been associated with sepsis in up to 8% of patients in whom they are introduced. Similar experiences have been recorded when percutaneous peripheral lines, "cutdowns" and subclavian lines have been employed (21–23). The risk of infection is frequently related to the length of time over which these devices remain in place, and the degree of care exercised in their management (7), but not to the length of the catheter or to the presence of phlebitis. The organisms responsible for infections that follow the use of catheters, shunts and "lines" are most often Staph. epidermidis, diphtheroids, and a variety of Gram-negative bacteria (7, 20), all of which are common constituents of the indigenous microflora of the skin. The mechanism for the introduction of these organisms into the blood stream appears to be migration from the dermal surface through the catheter or "lines." For this reason, attempts have been made to prevent intrusion of organisms into the circulation by applying various antimicrobial agents locally at the site at which the instrument enters the skin. Although a favorable prophylactic effect has been reported by some, others have failed to note a salutary effect of this procedure (22, 24). It has also been suggested that the inclusion of antibiotics such as penicillin G or nafcillin into the fluids administered through catheters may decrease the incidence of colonization and, by inference, the risk of infection (20).

Infections occurring in patients in whom polyethylene catheters or other "lines" have been introduced intravenously are not always related to these instruments, which may serve only as the route by which microorganisms gain entry into the circulation. The fluids that flow through such tubes have been implicated in several large outbreaks of hospital-acquired sepsis. These have been associated with the use of contaminated bottle-liner caps and defective autoclaving equipment (25, 26). The bacteria responsible for infections related to these have, as a rule, been uncommon causes of diseases, a fact that has made it relatively easy to define the pathogenesis of such epidemics. The organisms most frequently recovered from patients who have become infected following the administration of such fluids have been Enterobacter cloacae and other members of the tribe Klebsiella (25). The reason for this is the ease with which these bacteria multiply rapidly in many fluids maintained at room temperature; other common pathogens such as coagulase-positive staphylococci, Pseudomonas and E. coli do not thrive in such an environment (27). In addition to bacterial contamination of fluids prior to their use, organisms may be introduced during the administration of fluids; in this case the bacteria involved are frequently those that are present in the hospital environment and include Pseudomonas, E. coli, Klebsiella and Serratia (28). Although rare, infections have followed the administration of whole blood, blood products and platelets; these have been due to psychrophilic (cryophilic) bacteria including Pseudomonas and coliforms (29).

The recent development of total parenteral nutrition (hyperalimentation) (TPN) has created new problems related to infection, presently the most common complication of this therapeutic modality. Sepsis has been observed by some to develop infrequently in association with TPN, when the most meticulous care has been exercised in insertion of the intravenous catheter, preparation of the solutions and infusion of the fluid. However, the rate of infection has been reported to be as high as 27% in some instances (30). While both Gram-negative and Gram-positive bacteria have been involved in TPN-associated sepsis, species of Candida appear to be the commonest organisms (30, 31). The incidence of candidal infection has been recorded as high as 54%; this is very different from the risk that accompanies the use of other solutions. Although the specific reasons for the predisposition to invasion by yeasts and fungi have not been elucidated, it has been suggested that contributing factors may be (a) the debilitated state common to all patients requiring TPN, (b) administration of corticosteroids and antibiotics, (c) the topical application of antibacterial agents, (d) the ability of Candida to multiply in the solutions employed in TPN (7, 32), and (e) the commonly present hypophosphatemia that leads to decreased levels of ATP in phagocytes and dimunition in chemotaxis and effectiveness of phagocytosis (33).

Despite the fact that, in some instances, it is difficult to identify catheters, "lines" and various solutions as the source of a particular episode of infection because other predisposing factors may be present simultaneously, these instruments and fluids must always receive the most serious evaluation in relation to the pathogenesis of the infectious process. It is important to culture all apparatus as well as solutions in such situations. If infection has developed but its source cannot be identified immediately, it is good practice promptly to change all components of the system used for intravenous infusion. When the problem involves primarily colonization of the apparatus, especially the tip of the catheter, removal of this usually results in clearance of the organisms from the blood. This is especially true of candidemia which may persist for days or even weeks without clinical evidence of active infection when the tube lying in the circulation is contaminated. Removal of the catheter usually results in rapid disappearance of the organisms from the blood stream. If, however, the yeasts are recovered from the circulation repeatedly after removal of the catheter, and particularly if there is evidence of a constitutional reaction or localized disease, appropriate chemotherapy based on the nature of the organism is mandatory.

Arteriovenous Shunts. Although hemodialysis has greatly prolonged the lives of many patients with renal failure, serious and often life-threatening bacterial and fungal infections may supervene during the course of prolonged management with this procedure. That this should be a problem is predictable on the fact that the insertion of the arteriovenous shunt breeches the cutaneous-vascular barrier and opens it to invasion by organisms. Infection of such shunts is the most important complication of this mode of dialysis (34). Unlike many instances of catheter-associated infections in which the site of insertion of the instrument frequently appears normal, those related to arteriovenous shunts are often accompanied by localized pain, redness, edema, draining sinuses, extrusion of the shunt and pseudoaneurysm (35). Among the organisms recovered from shunts cultured prior to institution of dialysis are Staph. epidermidis (12%), Staph. aureus (7%), Strep. fecalis (0.7%), E. coli (0.6%), diphtheroids and yeasts (1.1%) and Pseudomonas (0.4%) (36). Despite the presence of so many different microbial genera and species, the majority of infections are due to Staph. aureus and Pseudomonas, and most of the complicating bacteremias are caused by coagulase-positive staphylococci (37, 38). The bulk of the infections produced by Staph. aureus arise from skin, nose and upper respiratory tract, areas that these organisms are prone to colonize. However, cross-infections usually have their source in hospitalized patients but not in members of the hospital staff with whom they come in contact.

Distant septic complications secondary to local infection of shunts are not uncommon; unusual lesions associated with such spread are mycotic aneurysms, suppurative arthritis and osteomyelitis. Infections of bone may be due to coagulase-negative and -positive staphylococci and Pseudomas aeruginosa, organisms commonly responsible for infectious complications in the site at which the shunt has been placed (39). Both acute and subacute infective endocarditis due to Strep. viridans, enterococci or Staph. aureus may follow infection of the shunt site (40, 41). That shunts play a role in the pathogenesis of cardiac valvular infections has been demonstrated experimentally in dogs. Endocarditis has been noted to develop in 70% of these animals following creation of an arteriovenous fistula; the frequency of this infection is increased if the artificially established shunts are small in size or if they are contaminated with a small number of bacteria (42). The pathogenesis of the cardiac lesion is thought to be trauma to the valve leaflets resulting from the increased work of the heart imposed by the arteriovenous fistula. Septic pulmonary emboli may also follow infection of the shunt, although local signs of involvement are not always present. The organisms responsible for the pulmonary infections are Staph. aureus and others known to colonize the shunt itself (43, 44). Manifestations at the site of the arteriovenous fistula are not present when the infectious process lies deep in the cannulated blood vessel; manipulation of the shunt may produce dislodgement of the emboli.

Effective treatment of infections of arteriovenous shunts and complicating metastatic disease requires the administration of large doses of appropriate antimicrobial agents and removal of the shunt; if endocarditis supervenes and hemodynamic problems develop, replacement of the infected valve by a prosthesis is often necessary. Therapeutic approaches that have not included removal of the arteriovenous shunt are usually unsuccessful (43).

Ventriculoatrial Shunts. Ventriculoatrial shunts (VAS) with the valve placed either proximally (Spitz-Holter) or distally (Pudenz-Heyer) are highly effective in the treatment of hydrocephalus, and appear to be the most physiologic approach to management of this problem. The combination of a reservoir that makes it possible to sample fluid, a subcutaneously situated catheter and a one-way valve provides unidirectional flow of cerebrospinal fluid from cerebral ventricle to cardiac atrium. In addition to problems related to blockage of the shunt, improper selection of patients, multiple pulmonary emboli, venous occlusion and vascular aneurysms, infections may also develop in patients with VAS. These may be primary or occur in the course of blockage of shunts or cardiovascular complications (45).

The incidence of VA shunt-related infections ranges from 6–23% (46, 47). Several infectious syndromes have been recognized. The frequency of these underscores the need for continuous microbiological monitoring, over months and years, of patients in whom such instruments have been placed. Both Staph. epidermidis and aureus have been recovered from shunts and have been responsible for infections appearing shortly after VAS have been implanted (5, 48, 49). The observation that organisms that usually populate the skin "regrow" within 10 minutes after cleansing of the skin, probably explains why staphylococci are so commonly involved in these infections. Disease caused by Staph. epidermidis tends to appear within 24 hours after insertion of the VAS, while that due to Staph. aureus develops somewhat later, sometimes after a month or more, and is usually associated with inflammation at the operative site (49). When Staph. epidermidis is involved, the infectious process may be very indolent, evidence of an inflammatory reaction may be absent and the cerebrospinal fluid may be normal in all respects despite the fact that it yields staphylococci when cultured. Because of these features, the presence of an infection may be overlooked unless proper cultures of the wound, shunt, blood and spinal fluid are made. Late complications are anemia, splenomegaly and bacteremia, findings that may lead to failure of recognition of the primary site of infection by the physician.

In addition to infections that develop shortly after insertion of VAS, others may not appear until more than a month after placement of the instrument (47, 50). The commonest cause of these in Staph. epidermidis; H. influenzae, Staph. aureus; group A streptococci have also been implicated. The clinical manifestations are primarily anemia, splenomegaly and fever. The pathogenesis of these late processes may be entrapment by the tip of catheters of organisms that intrude into the blood stream during the course of transient bacteremias. The valve within the shunt is regularly colonized (49). Colonization of VAS may persist without provoking dissemination of the organisms from the local site and infection does not develop. Cultures of VAS removed at the time of revision in patients with negative blood and spinal fluid cultures have revealed the presence of bacteria when the instruments have been in place for 1 to 48 months (46). Coagulase-negative staphylococci have been recovered most frequently, but diphtheroids have occasionally been present. Whether this represents merely contamination or a situation that prevails prior to the establishment of indolent bacteremia remains to be determined.

Some unusual infections of VAS appear to be related to the uncommon situation in which the catheter has been placed in close proximity to the tricuspid valve for a prolonged period. This may predispose to the development of thrombi, sites that are later colonized by organisms during the course of transient bacteremias. This may lead to the development of endocarditis that often involves the right side of the heart and is complicated by multiple septic pulmonary emboli and mycotic aneurysms. The appearance of repeated bouts of pneumonia in a patient with ventriculocatrial shunt should suggest the possibility of right-sided infective endocarditis, even when blood cultures are sterile (51).

Optimal therapy of infections of shunts in which bacteremia is a component is still a matter of controversy. It has been amply documented that prolonged treatment with antibiotics alone, even when these are active against the offending organism, is often ineffective (48, 49, 52). The rate of cure of this kind of disease with antibiotics alone has been reported to be less than 9% (49, 52). The reasons for the high frequency of therapeutic failure is related to poor penetration of a number of antibiotics into the meninges, and the difficulty of sterilizing an intravascular foreign body. In some instances, intravascular infusion of antibiotics has supplemented treatment by other routes. This has resulted in an increase in cure to 33% in some groups of patients, while in others it has been noted that, although rapid sterilization of the sites of infection has been accomplished, recurrences develop when therapy is stopped (52). It appears at present that administration of large doses of an effective antimicrobial agent and removal of the shunt offer the best possibilities of cure (48, 49, 52, 53).

Infections in Patients with Leukemia

Patients immunosuppressed by disease or treatment and often by both are peculiarly susceptible to invasion by a variety of organisms, many of which are included in the category of opportunists because they have been considered essentially nonpathogenic in the past, and rarely have produced infection. In addition to the basic defects that increase susceptibility to infection, such individuals often require treatment with antimicrobial agents (frequently broad spectrum in nature), are subjected to intravenous placement of catheters and are treated with intermittent positive pressure breathing and other manipulations that expose them to the microbial populations present not only in their own indigenous microflora but also in the environment of the hospital. In most instances, multiple factors are operating simultaneously or serially to increase risks of infection, and it usually is very difficult to identify a single situation as the responsible one. The infectious processes that involve such individuals are often produced by specific organisms but differ in etiology and severity as well as prognosis from those discussed above. The phenomenon of immunosuppression, whatever its cause, is very often responsible for therapeutic failure despite the exhibition of large doses of highly effective antimicrobial agents. This is because of marked suppression or abolition of the normal functional activity of cellular and humoral defense mechanisms. The presence of organisms that have rarely been associated with potentially lethal disease in the past and have often been considered contaminants by microbiologists, has emphasized the need for consultation between persons in the laboratory and clinicians to evaluate the clinical significance of *any* isolate. In addition, a number of disorders are presently caused by very fastidious microorganisms that require very special methods of culture, isolation and identification. This emphasizes even more the need for microbiologists to be informed by physicians of the possible involvement of such genera and species so that the procedures required to recover them are carried out. It is not possible because of space limitations to discuss here all of the disorders characterized by immunosuppression and the infections that complicate their course. For this reason, the writers have elected to elaborate the problem only in a single such disease, leukemia.

Infections have replaced hemorrhage as the commonest cause of death in patients with various types of leukemia. Study of one group of 450 individuals with leukemia who expired and were studied at necropsy has indicated that 79% died *with* infection and 69% as a result of infection *alone* (4). In addition to an increased frequency of infectious disorders in such patients, there has also been a change in the types of disease that have occurred over recent years. Thus, broncho- and lobar pneumonia were the commonest complications in the 1940's (54). In the next decade, infections due to coagulase-positive staphylococci became prominent (55, 56). Quite recently, there has been a decrease in the incidence of staphylococcal disease so that it is now responsible for less than 5% of death in leukemic patients (4, 55). Despite this, this organism remains an important agent in infections developing in such individuals. Although the specific reasons for the decline in the frequency of disease due to staphylococci remain undefined, it is possible that this is related to the availability of new antimicrobial agents to which these organisms are highly susceptible. There has been a sharp increase in the frequency of infections and death secondary to invasion by Gram-negative bacteria in the past decade. Patients with leukemia appear to be particularly predisposed to bacteremia with Pseudomonas, an organism responsible for 20–50% of such episodes; the prognosis of this syndrome is poor, often in spite of the exhibition of therapy that, on the basis of in vitro studies, should be highly effective. Other Gram-negative bacilli such as E. coli, Serratia, and

Klebsiella are increasingly frequent causes of disease in leukemics and are often responsible for a fatal outcome (4, 57–79). These genera are often resistant to most of the presently available antibiotics. Their increased incidence has been related to the widespread use of the so-called broad-spectrum antimicrobial agents.

In addition to changes in the types of organisms responsible for infections in patients with leukemia, differences have also been noted in the nature of the primary site from which bacteria and fungi invade the blood stream. Some years ago, the commonest foci from which infections were disseminated were the upper respiratory tract and the kidneys (56) Recently, however, it appears that more important primary sites are the lungs and anorectal area (4). Most of the infections that have their origin in these and other sites are produced by members of the indigenous microflora of patients; in about 4% of these, the organisms have been acquired earlier from the hospital environment (60).

One of the most important determinants of the prognosis of infections in leukemics is the number of circulating granulocytes. Both the frequency and the severity of bacterial infections are directly related to the duration and degree of granulocytopenia (4, 58, 61, 62). Whether the decrease is related to the underlying disease or to therapy with cytotoxic agents appears to be of no importance. An absolute granulocyte count of 500–1,000 is critical in determining the risk of infection; more than 90% of episodes of sepsis occur when the number is lower than this (59, 62). Failure of the granulocytes to increase in number in the course of a superimposed infection is also associated with a poor outlook for recovery. Other poor prognostic factors include prior treatment with antimicrobial agents, concurrent administration of corticosteroids and infection developing during a relapse of the leukemia (4, 63, 64).

References

1. Clendening, L., Reinfection with Streptococcus hemolyticus in Lobar Pneumonia, Measles, and Scarlet Fever, and its Presentation. Am. J. Med. Sci., 156:575, 1918.
2. Finland, M., Peterson, O. L., and Strauss, E., Staphylococcic Pneumonia Occurring During an Epidemic of Influenza. Arch. Int. Med., 70:183, 1942.
3. Klainer, A. S. and Beisel, W. R., Opportunistic Infection: A Review. Am. J. Med. Sci., 258:431, 1969.
4. Levine, A. S., Graw, R. G. and Young, R. C. Management of Infections in Patients with Leukemia and Lymphoma: Current Concepts and Experimental Approaches. Sem. in Hematol., 9:141, 1972.
5. Forrest, D. M. and Cooper, G. W., Complications of Ventriculoatrial Shunts. J. Neurosurg., 29:506, 1968.
6. Turcotte, J. G., Infection and Renal Transplantation. Surg. Clin. N. Amer., 52:1501, 1972.
7. Maki, D. G., Goldman, D. A. and Rhame, F. S. Infection Control in Intravenous Therapy. Ann. Int. Med., 79:867, 1973.
8. Weinstein, L. and Musher, D. M. (edit.) Antibiotic-induced Suprainfection J. Infect. Dis., 119:663, 1969.
9. Ribble, J. C. A Mechanism for Bacterial Interference *In Vitro*. J. Immun. 98:716, 1967.
10. Weinstein, L. Modes of Action of Antibiotics on Bacteria and Man. N. Y. State J. of Med., 72:2166, 1972.
11. Smith, D. T., The Disturbance of the Normal Bacterial Ecology by the Administration of Antibiotics with the Development of New Clinical Syndromes. Ann. Int. Med., 37:1135, 1952.

12. Louria, D. B. and Kaminski, T., The Effects of Four Antimicrobial Regimens on Sputum Superinfection in Hospitalized Patients. Am. Rev. Resp. Dis., 85:649, 1962.
13. Tillotson, J. R. and Finland, M., Bacterial Colonization and Clinical Superinfection of the Respiratory Tract Complicating Antibiotic Therapy of Pneumonia. J. Infect. Dis., 119:597, 1969.
14. Seligmann, E., Virulence Enhancing Activities of Aureomycin on Candida Albicans. Proc. Soc. Exper. Biol. Med., 79:481, 1952.
15. Campbell, C. C. and Saslaw, S., Enhancement of Growth of Certain Fungi by Streptomycin. Proc. Soc. Exper. Biol. Med., 70:562, 1949.
16. Weinstein, L., Goldfield, M., and Chang, T. W., Infections Occurring During Chemotherapy. New Eng. J. Med., 251:247, 1954.
17. Weinstein, L., The Spontaneous Occurrence of New Bacterial Infections During the Course of Treatment with Streptomycin or Penicillin. Am. J. Med. Sci., 214:56, 1947.
18. Collins, R. N., Braun, P. A., Zinner, S. H., and Kass, E. H., Risk of Local and Systemic Infection with Polyethylene Intravenous Catheters. New Eng. J. Med., 279:340, 1968.
19. Druskin, M. S. and Siegel, P. D., Bacterial Contamination of Indwelling Intravenous Polyethylene Catheters. J.A.M.A., 185:966, 1963.
20. Zinner, S. H., Denny-Brown, B. C., Braun, P., Burke, J. P., Toala, P., and Kass, E. H., Risk of Infection with Intravenous Indwelling Catheters: Effect of Application of Antibiotic Ointment. J. Infect. Dis., 120:616, 1969.
21. Fuchs, P. C., Indwelling Intravenous Polyethylene Catheters. J.A.M.A. 216:1447, 1971.
22. Moran, J. M., Atwood, R. P. and Rowe, M. I.: A Clinical and Bacteriologic Study of Infections Associated with Venous Cutdowns. New Eng. J. Med., 272:554, 1965.
23. Bernard, R. W., Stahle, W. M. and Chase, R. M., Subclavian Vein Catheterization: a Prospective Study. Ann. Surg., 173:191, 1971.
24. Hoshal, V. L. Jr., Intravenous Catheters and Infection. Surg. Clin. N. Amer., 52:1407, 1972.
25. Center for Disease Control. Nosocomial Bacteremias Associated with Intravenous Fluid Therapy. U.S.A. M.M.W.R. (Suppl.) 20, 12 Mar. 1971.
26. Phillips, I., Eykyn, S. and Laker, M., Outbreak of Hospital Infection Caused by Contaminated Autoclaved Fluids. Lancet, 1:1258, 1972.
27. Guynn, J. B., Poretz, D. M., and Duma, R. J., Growth of Various Bacteria in a Variety of Intravenous Fluids. Am. J. Hosp. Pharm., 30:321, 1973.
28. Duma, R. J., Warner, J. F. and Dalton, H. P., Septicemia from Intravenous Infusions. New Eng. J. Med., 284:257, 1971.
29. Braude, A. I., Carey, F. J. and Siemmienski, J., Studies of Bacterial Transfusion Reactions from Refrigerated Blood: Properties of Cold-growing Bacteria. J. Clin. Invest., 34:311, 1955.
30. Curry, C. R. and Quie, P. G., Fungal Septicemia in Patients Receiving Parenteral Hyperalimentation. New Eng. J. Med., 285:1221, 1971.
31. Goldmann, D. A. and Maki, D. G., Infection Control in Total Parenteral Nutrition. J.A.M.A., 223:1360, 1973.
32. Deeb, E. N. and Natsios, G. A., Contamination of Intravenous Fluids by Bacteria and Fungi During Preparation and Administration. Am. J. Hosp. Pharm., 28:764, 1971.
33. Craddock, P. R., Yawata, Y., VanSanten, L., Gilberstadt, S., Silvas, S. and Jacob, H. S., Acquired Phagocyte Dysfunction. New Eng. J. Med., 290:1403, 1974.
34. Working Party on Hemodialysis Units. Infection Risks of Haemodialysis: Some Preventive Aspects. Brit. Med. J., 3:454, 1968.
35. Farooki, M. S., Gergely, N. F., McAnich, L. N., Coates, R. K. and Kimber, R. W., External Arteriovenous Shunts for Intermittent Longterm Hemodialysis: Five Years Experience. Can. Med. Ass. J., 10:1371, 1970.
36. McIntosh, C. S., Petrie, J. C. and MacLeod, M., Maintenance of Silastic-Teflon Shunts for Intermittent Hemodialysis. Brit. Med. J., 4:717, 1969.
37. Kaslaw, R. A. and Zellner, S. R., Infection in Patients on Maintenance Hemodialysis. Lancet, 2:117, 1972.
38. Kurunida, K. C. and Beven, E. G., Arteriovenous Shunts and Fistulas for Hemodialysis. Surg. Clin. N. Amer., 51:1229, 1971.

39. Leonard, A., Conty, C. M., Shapiro, F. L. and Raij, L., Osteomyelitis in Hemodialysis Patients. Ann. Int. Med., 78:651, 1973.
40. Ribot, S., Rothfeld, D. and Frankel, H. J., Infectious Endocarditis in Maintenance Hemodialysis Patients. Am. J. Med. Sci., 264:183, 1972.
41. Saldanha, L. F., Goldman, R., Adashek, K. N. and Maldar, D. G., Treatment of Bacterial Endocarditis Complicating Hemodialysis. Brit. Med. J. 3:92, 1972.
42. Lillihei, C. W., Bobb, J. R. R. and Visscher, M. D., The Occurrence of Endocarditis with Valvular Deformity in Dogs with Arteriovenous Fistulas. Ann. Surg., 132:577, 1950.
43. Goodwin, N. J., Castronuovo, J. J. and Friedman, E. A., Recurrent Septic Pulmonary Embolization Complicating Maintenance Hemodialysis. Ann. Int. Med., 71:29, 1969.
44. Schmidt, P., Zazgornik, J., Kobsa, H. and Katzaurek, R., Septicaemia and Pulmonary Embolism Complicating Maintenance Hemodialysis. Lancet, 1:1129, 1972.
45. Anderson, F. M., Ventriculocardiac Shunts. J. Pediatrics, 82:222, 1973.
46. Fokes, E. C., Occult Infections of Ventriculoatrial Shunts. J. Neurosurg., 33:517, 1970.
47. Cohen, S. J. and Callaghan, R. P., A Syndrome Due to the Bacterial Colonization of Spitz-Holter Valves. Brit. Med. J., 2:677, 1961.
48. Callaghan, R. P., Cohen, S. J. and Stewart, G. T., Septicaemia Due to Colonization of Spitz-Holter Valves by Staphylococci. Brit. Med. J., 1:860, 1961.
49. Schimke, R. T., Black, P. H., Mark, V. H. and Swartz, M. N., Indolent Staphylococcus albus or aureus Bacteremia After Ventriculoatriostomy. New Eng. J. Med., 264:264, 1961.
50. Shurtleff, D. B., Christie, D. and Foltz, E. L., Ventriculoauriculostomy-associated Infection: A 12-year Study. J. Neurosurg., 35:686, 1971.
51. Emery, J. L. and Hilton, H. B., Lung and Heart Complications of the Treatment of Hydrocephalus by Ventriculoauriculostomy. Surg., 50:309, 1961.
52. Shurtleff, D. B., Foltz, E. L., Weeks, R. D. and Lasser, J., Therapy of Staphylococcus epidermidis: Infections Associated with Cerebrospinal Fluid Shunts. Pediatrics, 53:55, 1974.
53. Perrin, J. C. S. and McLaurin, R. L., Infected Ventriculoatrial Shunts: A Method of Treatment. J. Neurosurg., 27:21, 1967.
54. Kirshbaum, J. D. and Preuss, F. S., Leukemia. Arch. Int. Med., 71:777, 1943.
55. Frei. E., Levin, R. H., Bodey, G. P., Morse, E. E. and Freireich, E. J., The Nature and Control of Infections in Patients with Acute Leukemia. Canc. Res., 25:1511, 1965.
56. Silver, R. T., Utz, J. P., Frei, E. and McCullough, N. B. Fever, Infection and Host Resistance in Acute Leukemia. Am. J. Med., 24:25, 1958.
57. Hersh, E. M., Bodey, G. P., Nies, B. A. and Freireich, E. J., Causes of Death in Acute Leukemia. J.A.M.A., 193:105, 1965.
58. Hughes, W. T. and Smith, D. R., Infection During Induction of Remission in Acute Lymphocytic Leukemia. Cancer, 31:1008, 1973.
59. Umsawasdi, T., Middleman, E. A., Luna, M. and Bodey, G. P., Klebsiella Bacteremia in Cancer Patients. Am. J. Med. Sci., 265:473, 1973.
60. Schimpff, S. C., Young, V. M., Greene, W. H., Vermeulen, G. D., Moody, M. R. and Wiernik, P. H., Origin of Infection in Acute nonlymphocytic Leukemia. Ann. Int. Med., 77:707, 1972.
61. Bodey, G. P., Rodriguez, V. and Whitecar, J. P., Severe Infections in Leukemic Patients: An Approach to Antibiotic Therapy. Adv. in Mgmt. of Pseudomonas and Prot. Inf. Exerta Medica, 65-78, 1969.
62. Bodeg, G. R., Buckley, M., Sathe, Y. S. and Freireich, E. J., Quantitative Relationships Between Circulating Leukocytes and Infection in Patients with Acute Leukemia. Ann. Int. Med., 64:328, 1966.
63. Viola, M. V., Acute Leukemia and Infection. J.A.M.A., 201:923, 1967.
64. Miller, S. P. and Shanbrom, E., Infectious Syndromes of Leukemias and Lymphomas. Am. J. Med. Sci., 246:420, 1963.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 1, January-February, 1977
Printed in U.S.A.

Computers and Clinical Microbiology: Perspectives and Applications

DANIEL AMSTERDAM, PH.D.

The computer has pervaded every aspect of our life. Its uses have ranged from the apocalyptic to the trifling and no doubt its influence falls somewhere in between.

Life has been defined as an information processing system—a hierachy of functioning units—that has acquired through evolution the ability to store and process the information necessary for its own accurate reproduction. Similarly, the intellectual compartmentalization of man requires an information-processing directive toward orderliness. No doubt this is inherent in our makeup and stems from thermodynamic theory in that living systems constantly drive in the direction of increasing organization. In an environment in which all about us operates on the entropy maximum principle, a disorganizing principle, we constantly move in the direction of increasing organization. Hence, the imperative to organize our thoughts, ideas, and data; and the need for transmitting them requires additional assistance.

Our need to store, analyze, and communicate information was embodied in an experiment which took place in November, 1974. Radio astronomers beamed a three-minute radio message toward the Messier 13 Galaxy, light years distant from earth. Part of that transmission contained information about us and our galaxy: the chemical composition and graphic illustration of DNA; and the Earth's population and location in the solar system. The information for the message was encoded in binary numerical symbols—an indication of the anticipated universality of the binary code.

The idea of a computer as a brain is not entirely appropriate. Basically, the computer is a rapid calculating machine which has incorporated the developments of the electronic industry as a natural outgrowth of the desk-type calculator. Operating at enormously increased speeds, the computer lends itself to many applications of which computing is only a minor role. In addition to performing high-speed calculations, a computer can store vast quantities of information. If one were to make a human analogy on this effort, one could think of this function as memory. A number of applications which will be discussed make use of this rapidity which information can be stored and retrieved, or compared with recently acquired information. This type of activity is called data processing. The United States Bureau of the Budget has defined data processing as: "The preparation of source media which contain data or basic

From the Department of Microbiology, Isaac Albert Research Institute and Kingsbrook Jewish Medical Center, Brooklyn, N. Y. 11203.

Requests for reprints should be sent to: Dr. Daniel Amsterdam, Chief of Microbiology, Kingsbrook Jewish Medical Center, Rutland Road & East 49th Street, Brooklyn, N. Y. 11203.

elements of information, and the handling of such data according to precise rules of procedure to accomplish such operations as classifying, sorting, calculating, summarizing, and recording."

Computers are capable of performing prodigious tasks for men. With autonyms like PROPHET (1) and MIRACLE (2) (Multidisciplinary Integrated Research Activities in Complex Laboratory Environments), their capabilities are awesome. Computers have directed men in space, guided their destination and monitored their performance en route. They produce weather forecasts in advance, analyze stock market reports, and for industrial and commercial enterprises have proven invaluable in the production, codification, and presentation of information so that an accurate base is provided for decision-making. In their predictive capacity the reader is reminded of the quantitative study conducted by an MIT group. The study entitled, "The Limits of Growth" or more popularly the "doomsday report" involved the production of computer models for global economic trends based on five factors—food, population, pollution, resources, and capital. The report's conclusion was, "disaster within the next century." Detracters of this research pointed to an axiom of computer life—"garbage in equals garbage out."

Although currently approaching their fourth generation of development, the association of computers and the microbiologist is still in its nadir. Evidently, the generation times were exceedingly short or were spawned by some astro-fissionary process, because many of us were unaware of the first three generations. The major thrust of this paper will be directed toward the data processing capability of computers. Two aspects: their applications as a tool for those studying infectious diseases; and as an aid to epidemiologists in tracing sources of infection will be underscored. Additionally, the use of computers for identifying bacteria will be discussed.

Basic Concepts: General considerations

Computers are essentially numeric machines which can read numbers and act upon them. For this electronic device the code is represented in the form of a voltage level or a magnetic state and a number is represented in the computer by a series of switching circuits. It is the sequence of off and on which represents a code or number.

Computers are directed by human specialists in the form of programs and systems they use to instruct the computer. It is the program which gives the computer direction and the system which organizes the sequence of programs. It is the function of a system analyst to establish the type and level of input information, the degree, volume, and timing of required results, and then decide upon the best method of converting input to output from both a computer and human viewpoint. The resultant of the system analyst's effort is a system specification, which describes a series of stages through which the input data must pass in order to produce the desired results. Each stage represents the framework of a program. This report is then passed on to the programmer who has to convert the human-readable document into a series of logical steps that the computer can execute.

The numeric instructions which constitute the machine, that is, the programming language for the computer, is known as machine code. Although computers can readily handle this type of programming, the low-level language approach as it is called, is the most elegant, and requires an enormous effort by non-computer-oriented individuals, since it is organized along the lines of the computer's actual operations. This contributed to the advent of high-level programming languages organized along the lines of human thought. The world of commerce has common functions to perform and has devised COBOL (COmmon Business Oriented Language), utilizing key words in a basic form of English which the computer recognizes and translates. Mathematicians work in algorithms and devised ALGOL (ALGOrithmetic Language) for their use. Scientists needed to process complicated formulas by computer, so they devised FORTRAN (FORmula TRANslation) which uses accepted standards of formula construction for its conversions. The advent of these high-level languages has made possible the widespread applications of computers.

Computer Components: In the preceding, various parts of the computer have been noted without actually identifying them. Digital computers share five common components. Sequentially, there is an input unit which translates human produced information into machine-usable language. In the computer, information and instructions are sent to the second component, the memory, to await recall by the central unit. The central or control processing unit (CPU) controls the flow of information to the appropriate unit. Data can then be channeled to the arithmetic or logic unit to make the required calculations. When computations are complete, the output unit transforms the computer's electrical signals into records that people can read.

A computer system performs four distinct functions: input of data; processing of that data; storage of results; and output of results. The functions that most concern the applications of computers as related to microbiologists would be the input of data, and the output of results. These aspects are achieved by interfacing, or plugging into the central processor a series of peripheral devices which perform these functions while remaining under the control of the CPU. Interfacing may be thought of as the joining of members of a group (e.g., people, instruments) in such a way that they are able to function. Any component which stores information for the central unit must have the means of transferring data to and from it and can be categorized as an input/output device; and any device forming an interface between the human element and the computer can be thought of as an input/output element.

Binomial States and Codes: Computer components function in binary states; they can indicate only two possible modes. In the digital or binomial world one encounters the problem of languages and a concomitant need to translate one digital language (code) into another. Historically and conceptionally man has been taught to use and think in terms of decimal arithmetic in which the integers zero through 9 are used along with powers of 10 in order to represent any number desired. The simplest digital code is a two-state or binary code which consists of only two marks. For convenience the marks chosen are the decimal equivalent of zero and one; a "logic 0" and a "logic 1". In symbolic logic the symbols "A" and $\bar{A}$ (not A) are used. A comparison of the progression in binary and decimal system is shown in Table I. In these positional systems the value from right to left in the decimal is: ones (10^0); tens (10^1); hundreds (10^2), etc. In the binary system from right to left the value is: the ones (2^0); twos (2^1); fours (2^2); eights (2^3) etc. Numbers larger than one are generated by a binary number system that is based upon the radix (powers) of two (Table I). For example the number 10101_2 where the subscript "2" represents the binary system is equivalent to reading from left to right $(1 \times 2^4) + (0 \times 2^3) + (1 \times 2^2) + (0 \times 2^1) + (1 \times 2^0)$ which is equivalent to 21 in decimal notation. Similarly, the binary numbers 11101_2, 1000_2 and 101_2 represent in decimal notation, 29, 8, and 5 respectively. Although almost all electronic systems operate with two conditions or states, and therefore perform operation using binary arithmetic, it is clear that individuals are more reasonably used to decimal arithmetic. In view of this, it is common practice to encode a decimal number into binary form and have the electronic circuitry operate upon the resulting binary number. Finally, when a readout or output is desired, one decodes the binary numbers generated back into decimal form. Although a computer both encodes decimal numbers and decodes binary numbers stored in its core, a laboratory instrument only needs to decode binary information generated during the course of analysis.

The encoding and decoding process is not restricted simply to decimal numbers. It is equally important to be able to encode the alphabet into digital form as is done for example by teletypewriter. The object, therefore, with digital code is to encode numbers, alphabets, control functions, keyboard operations, and/or symbols in digital form, a task which is feasible in most

TABLE I

Numerical Progression in the Decimal and Binary System

Decimal		Binary			
10^1	10^0	2^3	2^2	2^1	2^0
	0	0	0	0	0
	1	0	0	0	1
	2	0	0	1	0
	3	0	0	1	1
	4	0	1	0	0
	5	0	1	0	1
	6	0	1	1	0
	7	0	1	1	1
	8	1	0	0	0
	9	1	0	0	1
1	0	1	0	1	0
1	1	1	0	1	1
1	2	1	1	0	0

Western countries but would be considerably more difficult in Oriental cultures.

For laboratory instrumentation the most popular digital code for encoding decimal numbers is the 8 4 2 1 code, or binary coded decimal (BCD) which is in effect a simple four bit code that starts at 0000_2 and terminates at 1001_2, the binary equivalent to the decimal integer 9. A similar device is the 4 2 2 1 code (Table II). Later we will see how the BCD has been applied to the computer assisted identification of bacteria.

Input/Output Media and Devices: These are the means by which the basic facts of a problem are fed into the computer and information is received from it. The media for this data representation include: punch cards; paper tape; magnetic tape; optically recognizable characters; magnetic ink characters; display screen images, etc. Each medium requires a code or specific arrangement of symbols to represent data and an associated device (machine) to sense or read information from the recording medium.

Punch cards (Fig. 1) contain places for 80 columns and each column provides 12 possible positions in row or rows in which holes can be punched. Ten of these represent the numbers 0 to 9 and there are two additional positions frequently referred to as X and Y positions, in which additional information can be punched. Various arrangements of these cards (Fig. 1 and 2) have been designed for specific microbiological applications. Although cards are available in another size, the 80-column cards have been most successful. The columns on the card are often divided into convenient smaller groups called fields. Numbers within a field embody a special significance and appropriate headings can be printed on the area. The 80-column punch card has been most successful although a 96-column card, one-third the size which can hold 20 percent more information, is available for use on smaller, simpler equipment (IBM System/3).

Usually cards have to be punched by hand from information on original documents. This can be done with a simple, mechanically operated punch with 12 keys or as is more common with a typewriter keyboard electronically connected to the punch. Accuracy of the card punching is essential, and it is necessary to verify the punched card. Verification can be carried out by

TABLE II

Digital Codes for Encoding Decimal Numbers

Decimal number	8 4 2 1	4 2 2 1
0	0000	0000
1	0001	0001
2	0010	0010
3	0011	0011
4	0100	1000
5	0101	0111
6	0110	1100
7	0111	1101
8	1000	1110
9	1001	1111

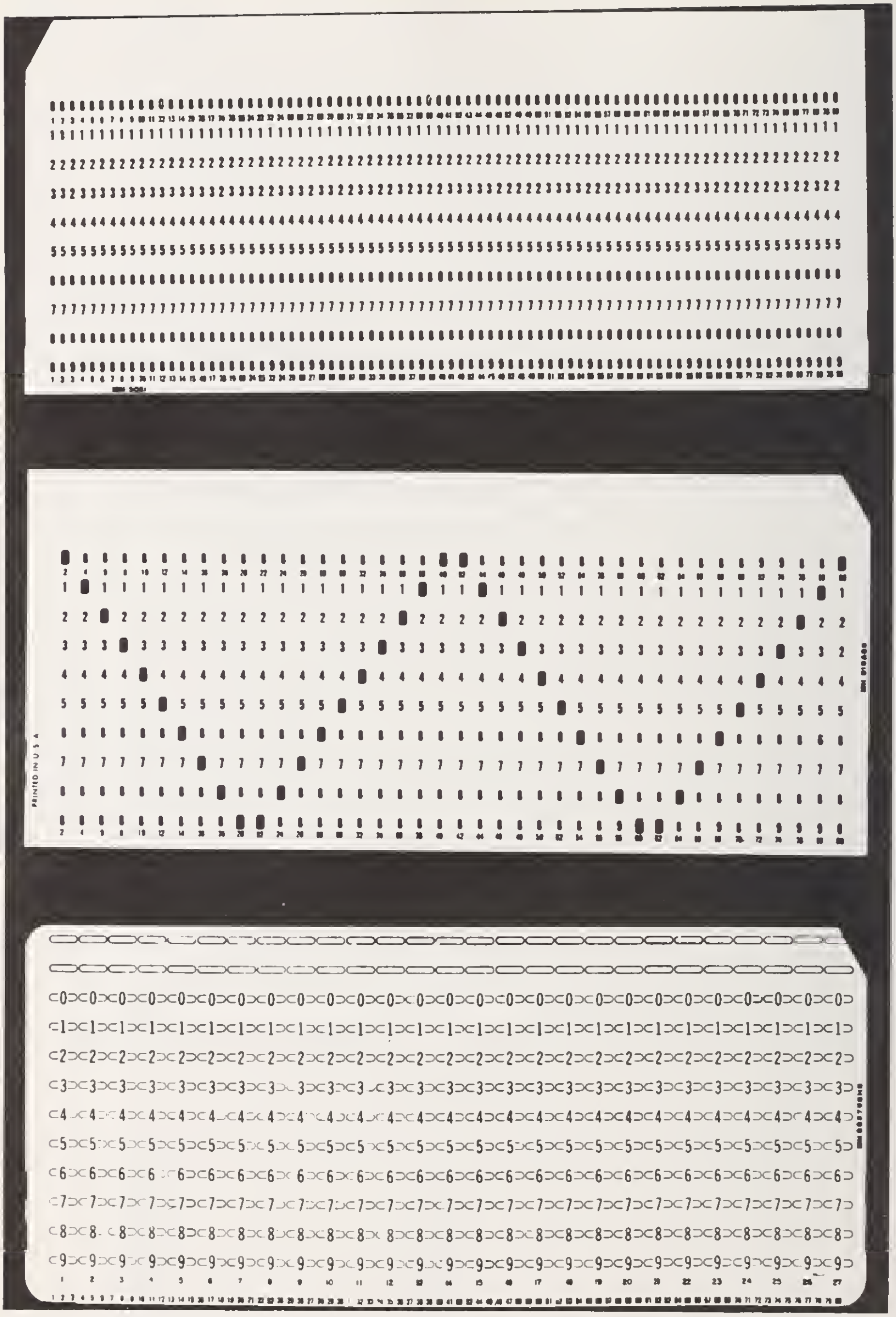

IBM 5081
PRINTED IN U S A

FIG. 1. Various IBM cards. Top to bottom: standard 5081 punch card; prescored Port-A-Punch card; and a mark-sense card.

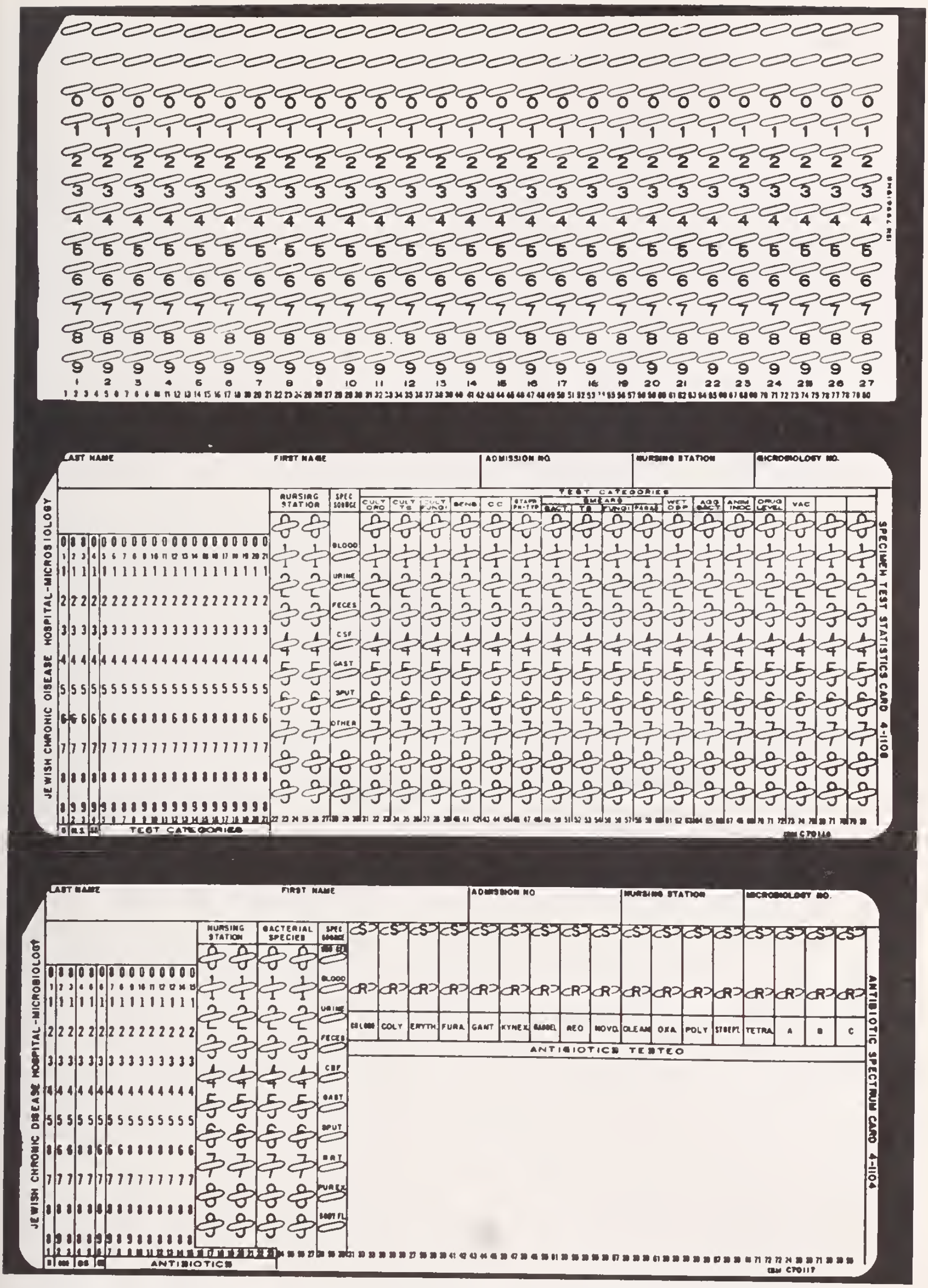

LAST NAME
FIRST NAME
ADMISSION NO.
NURSING STATION
MICROBIOLOGY NO.
TEST CATEGORIES
SPEC SOURCE
BLOOD
URINE
FECES
CSF
GAST
SPUT
OTHER
CULT ORD
CULT TB
CULT FUNGI
SENS
CC
SMEARS
BACT.
TB
FUNGI
PARAS
WET DEP
AGG BACT
ANIM INOC
DRUG LEVEL
VAC
JEWISH CHRONIC DISEASE HOSPITAL-MICROBIOLOGY
SPECIMEN TEST STATISTICS CARD 4-1108
BACTERIAL SPECIES
ANTIBIOTICS
ANTIBIOTICS TESTED
COLY
ERYTH
FURA
GANT
KYNEX
NEO
NOVO
OLEAN
OXA
POLY
STREPT
TETRA
A
B
C
ANTIBIOTIC SPECTRUM CARD 4-1104

FIG. 2. IBM mark-sense cards. Top to bottom: unspecified card; a preprinted card for sorting total test distribution; and a preprinted card for codifying antimicrobial susceptibility patterns and scatter of bacterial isolates.

repunching the card. Any discrepancy between the keys operated by the verifier and the characters punched in the original card will produce a warning and eject the card for rechecking. A variation of the standard 5081 card is the Port-A-Punch card (Fig. 1) on which prescored rectangular holes are punched out with a hand-held stylus.

Cards are "read" by detecting the presence or absence of a hole by an electrical contact or by means of a photoelectric cell. Cards can be punched in binary notation but usually they contain information in decimal form and this needs to be encoded into the binary format before it can be processed by the computer. Because of the decoding process and because feeding and reading cards is slow for modern computers the use of punch cards represents an inefficient means of using the computer.

Compared to cards, paper tape represents a fast means of presenting information. Whereas cards can be read at 400 characters per second, speeds up to a thousand characters per second can be achieved by this input device. Verification and accuracy are equally important when using paper tape.

Optical character recognition (OCR) is an input mechanism for source documents which precludes the time-consuming and error-prone punching phases. An optical system screens the input characters which are converted by appropriate electronics into the correct code for entry into the computer network. The drawbacks of this system are its high cost, the restricted kinds of typefaces which can be recognized, and the relatively slow time in which OCR characters can be read.

Most of the input elements noted above can also be used as output devices and therefore, punch cards and paper tape represent output formats. Of course, the most popular kind of output devices are printers and several variations of these are available.

Peripheral devices can act as input and output units. They have their own program in the computer which enables the operator to interrogate the computer files and receive an immediate response. Because of this facility they are said to be "on line" to the computer. The teletypewriter is the original on-line device. A printing keyboard not dissimilar to a typewriter in appearance and identical in concept is used. The teletypewriter is either linked directly to the computer if local, or linked to the computer in another part of the country by telephone lines. The application of the teletypewriter represents ultimate usage in that it is possible to make inquiries and transmit replies to the computer in fractions of a second so the operator receives an immediate response.

A more recent development in on-line equipment is a visual display unit using cathode ray tubes (CRT). It is based on a method identical to the teletypewriter except that ribbon and tape are replaced by a small television receiver screen on which the characters are reproduced. Such devices are expensive and require fairly large computers to operate, but their inherent advantages are that there is no need for punching and verifying since error checking can be made on a visual basis. With CRT display units one can gather facts instantly that are truly up to date which can then be used for decision-making purposes. The reader may have been exposed to such devices in booking reservations for theaters and airlines; or observing fluctuating stock market quotations.

Applications

Some of the reasons for using computers are: to interface with existing patient documentation in use at an institution; to provide specimen request slips on which laboratory findings are recorded; to provide reports on all requests sent to the laboratory; and to codify the data obtained from laboratory results for analyses. The purpose of these aims would be: (a) more accurate reporting; (b) faster reporting; (c) reduction of clerical workload; and (d) ease of analysis of past results for reviewing the findings on a patient; quality controls; administrative purposes; and research purposes.

Many steps are involved in the handling of information between ordering the test request by the physician, and his examination of the final report. The numerous sequences include:

—completing the request.
—labeling the specimen.
—transmitting the request along with the specimen to the laboratory.
—linking the specimen to the request form.
—preparing laboratory work sheets.
—recording preliminary test result data.
—calculating the results.
—quality control check.
—linking the results with the report (request) form.
—linking the most recent results with past results.
—editing the report.
—transmitting the report to the appropriate patient location.
—attaching the report to the patient's chart.
—maintain a final copy of the report in the laboratory file.

Each of these events can be regulated by an integrated computer system and many institutions have successfully achieved this end for controlling the movement of specimens and billing patient accounts. Although issuing requests, transmitting reports, and maintaining patient accounts are worthwhile objectives, they will not be discussed further.

The goals for computer applications should aim to go beyond efforts to duplicate the usual request procedure. Microbiologists ought to anticipate other administrative and investigative needs to completely utilize the computer's capabilities.

Nungester (3) enumerated five objectives for identifying microorganisms. They are: (a) to determine rapidly the susceptibility to antimicrobial drugs; (b) to obtain information which may have prognostic value to clinicians; (c) to identify organisms in terms of their potential danger to individuals in contact with patients; (d) to aid epidemiologists in tracing sources of infections; and (e) to accumulate data of interest to those studying infectious diseases.

These objectives are clearly in agreement with the goals for using computers in clinical microbiology, and we shall see each of these and other applications in the proceeding pages.

The systems and applications which I shall discuss are those which can be generated in the microbiology laboratory without the constraints of a central program. The main objective is directed toward the analysis of previously obtained laboratory results. From recently collected laboratory data computers can generate three levels of information of primary interest to microbiologists and infectious disease investigators: information for licensing and accrediting organizations; information for internal auditing and accounting; (third-party payments); and information for clinical evaluation.

Bacterial Identification: In an early paper, Steel (4) indicated that classification was an art, and identification a science. Recent developments have diminished the disparity, but unfortunately many clinical microbiologists have approached the practice of identification with metaphysical zeal. The terms classification, identification, and diagnosis have been used in different forms but here the terms identification and diagnosis will be used synonomously. It is generally agreed that one has to classify before an identification can be performed. Identification should be contrasted with taxonomy or systematics which according to Simpson (5) includes classification, nomenclature and identification. Identification is the pragmatic arm of taxonomy.

Clinical microbiologists will probably be amazed to discover that they think in mathematical sets and with symbolic logic. This kind of reasoning occurs for every identification and the subsequent clinical correlation of bacterial diagnosis with laboratory data. These acts can be ascribed to exercises in deductive and inductive reasoning and can be described with appropriate mathematical diagrams and symbols. The branches of mathematics or philosophy used for these functions are called set theory and symbolic logic. They are about 125 years old.

In identifying microorganisms the clinical microbiologist forms the identification by taking the initial knowledge of the morphologic appearance of a single pure colony—friable versus butyrous—or a preliminary set of biochemical data and applying it to subsequent observations. From this initial data base he draws tentative conclusions, acts on the basis of them, performs additional tests, observes what happens thereafter and lets it confirm or refute his initial decisions. He then relates all these events back to the original observations, and uses the total outcome to integrate or augment his existing store of knowledge. Some of these processes he performs by conscious discipline using specific data, or overt classifications and delineated reasoning processes of which he is fully aware. He accomplishes others so quickly and almost reflexively that the process becomes subconscious or intuitive, leaving him unaware of exactly what he has done and how he has used his store of background and experience to form a new observation.

Man organizes his thoughts for logical reason in a way that resembles their organization of words for grammatical speaking. Like the rules of grammar, the laws of rational thought have been studied and established. Mathematicians and philosophers have constructed and illustrated the system of logic by which human reasoning is formed and communicated. The mathematical development of this kind of rational thought named after its founder George Boole who introduced it around 1850 is called Boolean Algebra. It deals with sets or collections (classes of objects) rather than single objects and contemplates the relations of the collection or classes. A set can be defined as a collection of objects or elements of which all possess some common defining property. Thus, the set of all bacteria of medical importance, the set of all Gram-negative bacteria, or the set of all Gram-positive bacteria. Every object contained in a set must have the characteristic property of the set, but may have many other properties as well. Different sets have different characteristic properties, but each set can contain many subdivisions, called subsets, each of which has its own characteristic property. Thus, the set of all Gram-negative rods is composed of the set of fermentative rods and the non-fermenters. The set of all fermentative Gram-negative organisms contain such subsets as the phenylalanine deaminase-positive and phenylalanine-negative taxa. It is readily evident that a particular Gram-negative organism may belong to many sets. However, all Gram-positive bacteria would be excluded from those particular sets and subsets.

Identification processes depend upon gathering adequate information for characterizing the known organism and numerous ways have been proposed for handling that information. Some are based on the use of dichotomous keys (also known as decision trees, flow charts, and the sequence approach); others on diagnostic schemes and tables; and a third, utilizes the simultaneous or pattern method. Classically, microbiologists have depended upon flow charts in making selections or identifications. The inherent problem with flow charts is that adherence must be absolute in regard to the presence or absence of a reaction to a particular substrate. If the unknown organism does not conform perfectly to the flow chart an error will inevitably result. Since the decisional tree bases the selection of each suceeding test on the previous test result, until the lowest branch is reached, each separating group becomes the weakest link depending upon the number of branches in the network, and is a potential source for possible breakdowns in the identification method. Further, most flow charts do not allow for biologic variations to occur as expressed by differing biochemical reactions of the organism. As a decisional tree represents a model of a diagnostic process it is also a "discrimination net" and, therefore, has holes.

Diagnostic keys and tables have a severe important limitation in that the specimen must belong within the group of organisms for which the scheme was devised, otherwise aberrant identification or failure to identify will result. Access to data processing systems could significantly expand the number of diagnostic characters. However, with keys and tables the investigator is restricted by memory to a limited number of indices for which he can recognize similarities and differences while making simultaneous comparisons. Because of these limitations Cowan and Steel (6) constructed a mechanical device called the Determinator for the compilation of suitable tables. Another mechanical approach for comparing characters of unknown and known microorganisms is to use punched cards. This can be done by hand or sorting methods as described by Schneierson and Amsterdam (7). The advantage of computers is that an almost limitless number of criteria which are part of the identification scheme can be stored in the core microbial memory of the computer. Microbiologists will be surprised to learn that these flow charts and schemes are suitable for examination purposes but they do not represent the manner in which we actually deliberate; we think in terms of sets.

The simultaneous or pattern recognition approach for identification of organisms tests the organism for a large number of characters at one time. The simultaneous method has the advantage of speed and the decreased likelihood of gross error if a single test is read incorrectly. However, it lacks the inherent orderliness of the sequential method. Assisted by a computer it can handle a vast number of test patterns. If fifteen characters are included in the matrix (table) for identification, then 2^{15} or 32,768 combinations are possible; an unwieldy number for any microbiologist to sort and recognize. An unresolved issue is whether 32,768 combinations represent true taxa.

Elements of the Test Set: Three elements are associated with each test set which must be considered before utilizing them in any approach in microbial identification. These are: the probability of positive or negative for each test; the separation value of the test (8); and last, the reproducibility of the tests.

All tests in diagnostic microbiology can be treated as a two-state, that is, the result of any test can be scored as either positive (1) or negative (0). therefore, the sum of the probabilities for a positive and a negative result for any given organism is equal to one. Usually tests are not universally (100%) positive or negative for a taxon. As the ratio approaches one-half (0.5) of positive to negative, the usefulness of a particular test becomes nil. One can calculate the probability of a set of results by multiplying the probabilities of individual test results (9). However, this assumes that the tests are statistically independent—an assumption which cannot be strictly justified but which is necessary usually in this kind of an approach. Usually probabilities greater than, or equal to 0.85 are classified as positive, whereas those equal to or less than 0.15 are negative.

Gyllenberg (8) described the concept of the "separation-figure" referred to as the S-value. It is obtained by multiplying the number of taxa yielding a positive result in a given test by the number giving a negative result (Table III). This product is equal to the number of pairs of taxa that can be separated by a particular test and represents the overall differentiating power of each test. It should be noted that although two tests rate high S-values they may separate only the same set of pairs. The S-value is not constant; it will vary depending on the set in which it is used. Twenty-one S-values of commonly used diagnostic tests for fermentative taxa are ranked in Table IV.

The third important characteristic of a test set is test reproducibility. Test error is most readily estimated by analysis of variance of replicates (10). When the average probability of an incorrect test is greater than 10%, serious

TABLE III

Calculation of S-Values[a]

Tests	Organisms				Number		S-value
	W	X	Y	Z	Pos.	Neg.	
a	+	+	+	+	4	0	0
b	+	+	–	–	2	2	4
c	+	–	–	–	1	3	3
d	–	–	–	–	0	4	0

[a] Separation-value = No. Pos. × No. Neg.

TABLE IV

Ranking of Some Commonly Used Diagnostic Indices Based on Separation Value[a]

Ranking No.	Test	Separation value (S) (max. = 784)	S as a percentage of maximum
1	Arabinose, acid production	726	93
2	Motility at RT	700	89
3	Rhamnose, acid production	696	89
4	ONPG (β-galactosidase)	660	84
5	Gas production from glucose	648	83
6	Sorbitol, acid production	625	80
7	Ornithine decarboxylase	624	80
8	KCN medium growth	616	79
9	Indole production	595	76
10	Lysine decarboxylase	580	74
13	Methyl red at RT	544	69
14	Arginine, dihydrolase	544	69
19	H_2S production (TSI)	473	60
20	Lactose, acid production	455	58
23	Simmons' citrate, growth	448	57
24	Methyl red at 37°C	442	56
26	Gelatin liquefaction within 5 days	414	53
29	Oxidase, presence	378	48
34	Urease, presence	342	44
38	Deamination of phenylalanine (PPA)	300	38
48	Nitrate reduction	0	0

[a] Adapted from Lapage *et al* (18); based on a total of 49 tests. RT, room temperature.

distortion of identification can result. This type of distortion must be judged against that due to sampling error, which predominates when the number of tests is small. Hence, numerical taxonomists advocate the use of as many tests as possible provided that the test error for any one is not too large (10). The upper limit to the permissible error on any one test is not defined.

It is necessary for the clinical microbiologist to know the reproducibility of any one test within his own laboratory. Most of us are unaware of this information. Inattention to test error will explain unsatisfactory results between laboratories. Theoretically, replicates should yield identical results in the same laboratory, but differences often occur. Factors which impair intralaboratory reproducibility are reading intervals (overnight, versus actual elapsed 18 or 24 hours); and variations in incubation temperature due to inaccurate temperature setting or fluctuations in temperature that occur from shelf to shelf within air convected incubators. The reproducibility of tests between laboratories is expected to be larger than within a laboratory. This is due to factors other than mentioned above. Variations can be due to batch or brand differences among culture media, inoculation techniques, and/or discrepancies between observing and reading results. As with all variations, statistical errors tend to accumulate rather than cancel out one another.

Computer-assisted identification: Since the first suggestions (11, 12) of the use of computers in bacterial identification, numerous investigators have made significant contributions (8, 9, 13–19). Only two states exist in the algebra of logic under which computers operate: yes or no; true or untrue; present or not present; they are represented by one and zero respectively. (Within the computer electronic logic these states refer to different voltage levels.) Binary logic is also representational of the qualitative manner in which diagnostic tests are interpreted. Hence computers seem ideally suitable for diagnostic evaluation. (Computers could handle multi-state reactions as well.) If an organism were tested for five biochemical attributes and the first three were positive and the last two negative, then the binomial result would be 11100, and 32 (or 2^5) combinations are possible.

Diagnostic kits designed for the identification of enteric bacteria use anywhere from six to twenty-one tests and express test results in a binomial manner. Stringent adherence to the sequence position of each reaction per the manufacturer's directions permits positive or negative results to be recorded along the line of a BCD code. A resulting number (in decimal format) encompasses the accumulated reactivity of the bacterium to the various biochemical substrates. Often the manufacturer supplies the user with an abbreviated matrix (table) of all the possible combinations. It is readily understandable that these tables would be abbreviated because for 21 tests, there would be 2^{21} or 2,097,152 listings. Additionally, the manufacturer usually offers a computer identification program based upon a most likelihood or Bayes' theorem identification approach. Once instructed with the decimal representation of the organism's biochemical profile, the computer converts it to the corresponding binomial index, searches the matrix program, and prints out an identification.

Although Bayes' theorem is readily derived from rules of mathematical theory of probability as a basic concept, detracters have not agreed with the controversial meaning of probability (20). Early application of Bayes' theorem was suitable for clinical diagnosis but was considered inappropriate for bacterial identification (13). The major reason for disallowing its use in Clinical Microbiology was a paucity of quantitative data. Friedman et al (19) overcame this problem by employing the Enterobacteriaceae since a considerable amount of test data was available for this group.

In the same moment that different probability theories (and concepts of prior and posterior probability) which ground computer-assisted programs of identification are contended, it is necessary to stand back and reflect. As investigators who have worked too long in a semiquantitative area, we are at once exceedingly pleased with the digital environment and binomial language in which we have been immersed. What could seem more profound than tagging a bacterium with a three-to-seven digit (decimal notation) autonym. It has seemingly conferred a sense of quantitative security to our efforts. Before automation (or even mechanization) of analytical techniques has been achieved, we have successfully analyzed and manipulated the data derived from conventional procedures.

What are these orthodox procedures? Estimates of interlaboratory test result variations indicated that brand and batch differences of media account for the major disparity (10). The media used are often compounded with chemically undefined complexes "gunks," inoculated with varying quantity of assumedly pure bacterial cells, incubated for unspecified lengths of time, and then, on the basis of color change, observed and interpreted subjectively. Thus, the first interface between test data and the computer is the human eye. The problem is further aggravated. Current models for computer identification rely on the entry of the accumulated records of sample organisms and/or reports from the literature in order to construct the matrix. If the data-dependent tests used for the computer tables are not identical to those supplied by the manufacturers then one would readily expect disparity between computer and conventional identifications. A positive aspect of this dilemma would result if clinical microbiologists could agree on a standard sequence set for identification of Enterobacteriaceae (and other groups). Then, the assignation of the decimal-derived binomial would signify specific biochemical reactivity without the often subjective name-tagging.

Analysis of Antimicrobic Susceptibility Test Data: Surveillance of Hospital Infection: The accumulated daily laboratory test results which report on the interaction of bacterial isolates to a variety of antimicrobial agents provide an immense data source which reflects both primary and nosocomial infectious disease events. It has prognostic value.

In 1967, Schneierson and Amsterdam (21) were first to report on the use of computer-assisted analyses of antimicrobic susceptibility data. A later study (22) described the relevant manner in which the susceptibility data could be used to advantage in a number of different applications. Although the systems described are initiated in the laboratory they could eventually be incorporated into a comprehensive plan. Because the data representation media which serves as computer input contains the bacterial isolate, the source of the isolate, the patient location within the institution, and the suceptibility, the information can be codified in several ways. Four primary reports can be generated; they are:

—The overall hospital antimicrobic susceptibility percentage.
—The susceptibility percentage according to specimen source.
—The susceptibility percentage within each patient location.
—The susceptibility percentage according to medical services.

The inputs previously noted can also serve to rpoduce a surveillance report of hospital infections. Cards can be sorted as to the location of a particular species, the species itself, and/or the source of the organism. The printout will indicate the number of organisms present in separate patient areas and distributed among different pathologic sources. This can alert the epidemiologist and the infection committee and pinpoint the source of nosocomial infection. Additionally, the input from susceptibility data can be used to follow a specified organism for surveillance purposes. The reports produced for this aim are:

—The distribution of a selected species according to specimen source.
—The distribution of a selected species according to medical service.
—The distribution of a selected species according to patient location.

If outpatient services are offered at an institution, then antimicrobic susceptibility patterns can be contrasted between the resident populations and the extrahospital population. Further, the susceptibility patterns can be grouped to indicate those strains resistant to multiple antimicrobics and potentially expressing resistant determinants. This would represent a statistical incidence of R factor in the institution. Clearly, whether or not R factors exist would have to be proved by the ability of the organism to transfer the resistance factor to a susceptible recipient. Antibiotic susceptibility data can also be coupled with information from the hospital pharmacy. The quantity (grams) of antimicrobic dispensed to various services could be an indicator of in-house selective pressure and cyclic fluctuations in susceptibility could be understood.

All of the foregoing applications have the following important benefits: reduction of the clerical workload and effort in the preparation of various reports, and presentation of timely informative summaries for the infection committee; the use of antibiotic susceptibility data for ordering antibiotics or predicting the capability of antibiotic activity; analysis of costs and performance on antibiotics; and provision for statistical trend analysis of organisms and effectiveness of treatment.

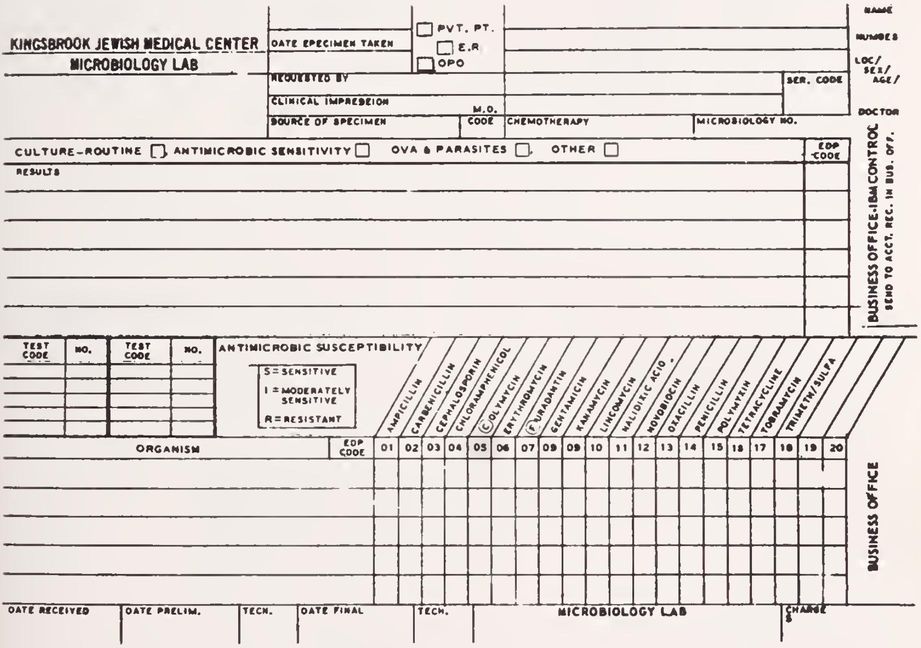
Total Test Statistics: As state and federal monies bear an ever larger part of the burden of the cost for maintaining the health of the community, detailed statistics will be required by these agencies for individual patient and hospital accounts, since it is common practice for these agencies to base their reimbursement on costs. Furthermore, information about the overall number and types of tests performed by the laboratory assumes ever increasing importance for accreditation by various professional groups and overseer agencies. The tabulated data can also support the laboratory requests for additional space, personnel and/or new equipment. For these reasons it becomes essential to know the total number of the different determinations performed and their distributions according to services, hospital locations, and the source of payment to equitably compensate the hospital and laboratory.

In our laboratory, tests used by the technologist for completing the diagnosis are detailed in Table VIII (22).

Computer-Compatible Reports: Alternative to the laboratory preparation of special IBM documents (Figs. 1 and 2), information can be keypunched directly from computer-compatible microbiology reports (Fig. 3) once appropriate master files are prepared. Master codes for microbial species, antimicrobics, specimen/sources, and test categories are listed in Tables V–VIII.

Additionally, these kinds of master files can be expanded so as to include such phrases as "No Growth," "More than 100,000 organisms/cc," etc. In the laboratory, the technician adds the appropriate code for the microbial species, source of specimen, and records the appropriate Bauer-Kirby result. Antimicrobic codes and other pertinent patient information are preprinted on the request. After completing the diagnoses a pressure-sensitive copy of the final report is transmitted to data processing for punching.

Future Aspects: As automated equipment becomes more prevalent in the clinical microbiology laboratory, a number of computer applications will be evident. Minicomputers (and now microcomputers) attached as peripheral devices to the output of recording instruments could play an important part in monitoring certain events, especially as relates to antimicrobic susceptibility data. Daily checks of quality control, on the conditions of the test, the media, and potency of antimicrobial agents would be possible. Additionally, susceptibility patterns of individual patients reported on a specific day could be compared with recent results for any trend. Also, as it is now considered good practice to test antimicrobial agents that are important for epidemiologic reasons but not for therapy, the on-line computer could edit the report so that the physician would receive results of the standard test group; whereas the laboratory file would contain all the data.



KINGSBROOK JEWISH MEDICAL CENTER
MICROBIOLOGY LAB

DATE SPECIMEN TAKEN
☐ PVT. PT.
☐ E.R
☐ OPD
REQUESTED BY
CLINICAL IMPRESSION
SOURCE OF SPECIMEN
M.D. CODE
CHEMOTHERAPY
MICROBIOLOGY NO.
SER. CODE
NAME
NUMBER
LOC/ SEX/ AGE/
DOCTOR

CULTURE–ROUTINE ☐ ANTIMICROBIC SENSITIVITY ☐ OVA & PARASITES ☐ OTHER ☐
EDP CODE
RESULTS

BUSINESS OFFICE-IBM CONTROL
SEND TO ACCT. REC. IN BUS. OFF.

TEST CODE	NO.	TEST CODE	NO.

ANTIMICROBIC SUSCEPTIBILITY

S = SENSITIVE
I = MODERATELY SENSITIVE
R = RESISTANT

AMPICILLIN	CARBENICILLIN	CEPHALOSPORIN	CHLORAMPHENICOL	Ⓒ OLYMYCIN	ERYTHROMYCIN	Ⓕ URADANTIN	GENTAMICIN	KANAMYCIN	LINCOMYCIN	NALIDIXIC ACID	NOVOBIOCIN	OXACILLIN	PENICILLIN	POLYMYXIN	TETRACYCLINE	TOBRAMYCIN	TRIMETH/SULFA		
01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20

ORGANISM
EDP CODE

BUSINESS OFFICE

DATE RECEIVED
DATE PRELIM.
TECH.
DATE FINAL
TECH.
MICROBIOLOGY LAB
CHARGE $

FIG. 3. Microbiology request/report form suitable as a data representation medium for IBM key punch input.

TABLE V

Microbiology EDP Codes
Microbial Species

01—Arizona sp.
02—Citrobacter diversus
03—Citrobacter freundii
04—Citrobacter sp.
05—Edwardsiella sp.
06—Enterobacter aerogenes
07—Enterobacter agglomerans
08—Enterobacter cloacae
09—Enterobacter hafniae
10—Escherichia coli
11—Escherichia sp.
12—Klebsiella pneumoniae
13—Klebsiella pneumoniae, var. oxytoca
14—Klebsiella sp.
15—Pectobacterium sp.
16—Proteus mirabilis
17—Proteus morganii
18—Proteus rettgeri
19—Proteus vulgaris
20—Proteus sp.
21—Providencia sp.
22—Salmonella sp.
23—Serratia liquefaciens
24—Serratia marcescens
25—Serratia sp.
26—Shigella sp.
27—Yersinia sp.
28—Aerobic Gram-neg., oxidase-neg. rods
29—Achromobacter sp.
30—Acinetobacter sp.
31—Ac. calcoaceticus var. anitratus (Herellea)
32—Ac. calcoaceticus var. lwoffi (Mima polymorpha)
33—Aeromonas sp.
34—Alcaligenes sp.
35—Chromobacterium sp.
36—Flavobacterium sp.
37—Moraxella sp. (Mima oxidans)
38—Pasteurella sp.
39—Pseudomonas aeruginosa
40—Pseudomonas maltophilia
41—Pseudomonas sp.
42—Vibrio sp.
43—Aerobic Gram-neg., oxidase-pos. rod
44—Bordetella sp.
45—Brucella sp.
46—Eikenella sp.
47—Hemophilus HB
48—Hemophilus influenzae
49—Hemophilus parainfluenzae
50—Hemophilus sp.

51—Neisseria gonorrhoeae
52—Neisseria meningitidis
53—Neissera sp.
54—Aerobic Gram-neg. coccus
55—Bacteroides corrodens
56—Bacteroides fragilis
57—Bacteriodes sp.
58—Fusobacterium sp.
59—Leptotrichia sp.
60—Anaerobic Gram-Negative Rod
61—Clostridium perfringens
62—Clostridium sp.
63—Anaerobic Gram-Positive Rod
64—Peptococcus sp.
65—Peptostreptococcus sp.
66—Anaerobic Gram-pos. coccus
67—Veillonella sp.
68—Anaerobic Gram-neg. coccus
69—Bacillus sp.
70—Corynebacterium diphtheriae
71—Corynebacterium sp.
72—Diphtheroids
73—Erysipelothrix sp.
74—Kurthia sp.
75—Listeria monocytogenes
76—Streptobacillus moniliformis
77—Aerobic Gram-pos. rod
78—Staphylococcus aureus
79—Staphylococcus epidermidis
80—Micrococcus sp.
81—Streptococcus pneumoniae
82—Streptococcus—Group A
83—Streptococcus—Group B or C
84—Streptococcus—Group D (Enterococcus)
85—Streptococcus—Group D (non-Enterococcus)
86—Streptococcus, alpha (viridans)
87—Streptococcus, gamma (viridans)
88—Other Streptococcus
89—Aerobic Gram-pos. coccus
90—Actinomycetes
91—Mycobacterium tuberculosis
92—Mycobacterium sp.
93—Nocardia sp.
94—Streptomyces sp.
95—Candida albicans
96—Candida sp.
97—Other yeasts or fungi
98—Other
99—
00—

TABLE VI

Microbiology EDP Codes
Antimicrobics

EDP Code	Antimicrobic	Primary Syllable Recognition Printout	EDP Code
01	ampicillin	AMPI	01
02	carbenicillin	CARB	02
03	cephalosporin	CEPH	03
04	chloramphenicol	CHLO	04
05	Colymycin	COLY	05
06	erythromycin	ERYT	06
07	Furadantin	FURA	07
08	gentamicin	GENT	08
09	Kanamycin	KANA	09
10	lincomycin	LINC	10
11	nalidixic acid	NALD	11
12	novobiocin	NOVO	12
13	oxacillin	OXAC	13
14	penicillin	PENI	14
15	polymyxin	POLY	15
16	tetracycline	TETR	16
17	tobramycin	TOBR	17
18	trimethoprim/ sulfamethoxazole	TMSX	18
19	amoxacillin	AMOX	19
20	ristocetin	RIST	20
21	spectinomycin	SPEC	21
22	streptomycin	STRP	22
23	triple sulfa	TSSS	23
24	vancomycin	VANC	24
25	other A	OTHA	25
26	other B	OTHB	26

TABLE VII

Microbiology EDP Codes
Specimen/Source

EDP Code	Specimen/source
1	Blood
2	Urine
3	Feces—Stool
4	CSF
5	Gastric
6	Sputum (including bronchial aspirates)
7	N & T/NP
8	Transudates (ascitic, peritoneal, etc.; body fluids other than blood or CSF)
9	Purulent Exudates
A	Other
B	Blood, Postmortem
C	Other, Postmortem
D	Inanimate

TABLE VIII

Microbiology EDP Codes
Test Categories

01—Culture, ordinary
02—Culture, TB
03—Culture, Fungus
04—Antimicrobic sensitivity
05—Colony Count
06—Staphylococcal Phage Typing
07—Smear, bacteria
08—Smear, TB
09—Smear, fungus
10—Smear, parasite
11—Wet preparation, ova and parasite
12—Agglutination, bacteria
13—Animal inoculation
14—Serum Drug Level
15—Serum Inhibition
16—Vaccine
17—Viral Study
18—Fungal Serology
19—Toxoplasmosis
20—Other Serology
21—Sterility Control
22—Other

Antimicrobic susceptibility patterns have been used as a means to identify bacterial isolates. Friedman and MacLowry (23) in a first attempt were able to achieve an 86% agreement with conventional identification. Although they indicated that accuracy was not of an order to replace orthodox methods of diagnosis, identifications utilizing antibiotic susceptibility data might be feasible.

The extensive use of computers could determine antimicrobic efficacy as relates to age, sex, and nutritional status. Other trends are those currently undergoing scrutiny by the National Institutes of Health's specialized computer resource (2). Data collected from this network could examine the modulating effects of various pharmacologic agents when administered with antimicrobials. Lastly, and perhaps ultimately, computers programmed with infectious disease models could predict with some certainty the outcome of the interaction between bacterium, drug, and host.

References

1. Harrington, R. B. and Giese, R. L.: MIRACLE—A Hierarchical Data Acquisition System for Laboratory Automation, Fed Proc **33**:2393, 1974.
2. Raub, W. F.: The PROPHET system and Resource Sharing, Fed Proc **33**:2390, 1974.
3. Nungester, W. F.: Contributions of Microbiology and Immunology to Medicine and Some Unfinished Business, Texas Rep Biol Med **21**:315, 1963.
4. Steel, K. J.: The Practice of Bacterial Identification, Symp Soc Gen Microbiol **12**:405, 1962.
5. Simpson, G. C.: *Principles of Animal Taxonomy*. Columbia University Press, New York 1961.
6. Cowan, S. T. and Steel, K. J.: A Device for the Identification of Microorganisms, Lancet **1**:1172, 1960.
7. Schneierson, S. S. and Amsterdam, D.: A Punch Card System for Identification of Bacteria, Am J Clin Pathol **42**:328, 1964.
8. Gyllenberg, H. G.: A Model for Computer Identification of Microorganisms, J Gen Microbiol **39**:401, 1965.
9. Lapage, S. P., Bascomb, S., Willcox, W. R., and Curtis, M. A.: Computer Identification of Bacteria. In: *Automation Mechanization and Data Handling in Microbiology*, Edited by A. Baillie and R. J. Gilbert Academic Press, New York 1970, pp. 1–22.
10. Sneath, P. H. A. and Johnson, R.: The Influence on Numerical Taxonomic Similarities of Errors in Microbiological Tests, J Gen Microbiol **72**:377, 1972.
11. Sneath, P. H. A.: The application of Computers to Taxonomy, J Gen Microbiol **17**:201, 1957.

12. Beers, R. J. and Lockhart, W. R.: Experimental Methods in Computer Taxonomy, J Gen Microbiol **28**:633, 1962.
13. Dybowski, W. and Franklin, D. A.: Conditional Probability and the Identification of a Bacteria; A Pilot Study, J Gen Microbiol **54**:215, 1968.
14. Payne, L. C.: Towards Medical automation, World Med Electronics **2**:7, 1963.
15. Rypka, E. W., Clapper, W. E., Bowen I. G., and Babb, R.: A Model for the Identification of Bacteria, J Gen Microbiol **46**:407, 1967.
16. Rypka, E. W. and Babb, R.: Automatic Construction and Use of an Identification Scheme, Med Res Engineering **9**:9, 1970.
17. Sneath, P. H. A.: New Approaches to Bacterial Taxonomy: Use of Computers., Ann Rev Microbiol **18**:335, 1964.
18. Lapage, S. P., Bascomb, S., Willcox, W. R., and Curtis, M. A.: Identification of Bacteria by Computer: General Aspects and Perspectives, J Gen Microbiol **77**:273, 1973.
19. Friedman, R. B., Bruce, D., MacLowry, J., and Brenner, V.: Computer-Assisted Identification of Bacteria, Am J Clin Pathol **60**:395, 1973.
20. Willcox, W. R., Lapage, S. P., Bascomb, S., and Curtis, M. A.: Identification of Bacteria by Computer: Theory and Programming, J Gen Microbiol **77**:317, 1973.
21. Schneierson, S. S. and Amsterdam, D.: A Manual Punch Card System for Recording, Filing, and Analyzing Antibiotic Sensitivity test results, Am J Clin Pathol **47**:818, 1967.
22. Amsterdam, D. and Schneierson, S. S.: Electronic Data Processing System for the Clinical Microbiology Laboratory, Appl Microbiol **17**:93, 1969.
23. Friedman, R. and MacLowry, J.: Computer Identification of Bacteria on the Basis of their Antibiotic Susceptibility Patterns, Appl Microbiol **26**:314, 1973.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 1, January-February, 1977
Printed in U.S.A.

Some Cautionary Considerations for the Automation of Clinical Microbiologic Procedures

HENRY D. ISENBERG, PH.D.

To date, the clinical laboratory has encountered automation of procedures concerned with static samples, that is, a specimen once obtained contains the cellular or chemical constituents of interest, subject to deterioration with time, but essentially removed from interaction with their source. Viable segments of microbial populations in specimens, on the other hand, are dynamic and while separated from their source, subject to constant change. While this major difference ought not to present an obstacle, the very nature of microorganisms cannot be ignored by those bent on using specific microbial attributes for a specific analytical or practical purpose. It is perhaps best to introduce the thrust of my concern by quoting one of Belloc's poems from the late nineteenth century:

> The Microbe is so very small
> You cannot make him out at all,
> But many sanguine people hope
> To see him through a microscope.
> His jointed tongue which lies beneath
> A hundred curious rows of teeth,
> His seven tufted tails with lots
> Of lovely pink and purple spots
> On each of which a pattern stands
> Composed of forty separate bands;
> His eyebrows of a tender green—
> All these have never yet been seen.
> But scientists who ought to know,
> Assure us that they must be so—
> Oh, let us never, never doubt
> What nobody is sure about.

Of course, everyone is aware of the fantastic advances made by modern science since Belloc scoffed at microbiology. Today, this derision no longer obtains; microbiology has spawned a whole series of disciplines, one of which has been in the forefront of solving the secrets of the genetic code. Today, no one is ashamed to model his messenger, ribosomal and soluble RNAs after a certain strain of Escherichia coli. But, it seems that in 1962, two very knowledgeable and outstanding microbiologists, Stanier and van Niel, stated: "Any good biologist finds it intellectually distressing to devote his life to the

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From the Long Islan i Jewish-Hillside Medical Center, New Hyde Park, N. Y. 11040.
Requests for reprints should be sent to: Henry D. Isenberg, Ph.D., Long Island Jewish-Hillside Medical Center, 270-05 76th Avenue, New York, N. Y. 11040.

study of a group that cannot be readily and satisfactorily defined in biological terms; and the abiding intellectual scandal of bacteriology has been the absence of a clear concept of a bacterium (1). Nothing has happened in the last decade to modify or soften this indictment. Thus, the biologist, more specifically the microbiologist, is confronted with his own "uncertainty principle" magnified appropriately for biological application and distorted by the complexities of cellular and organismal organization as well as lack of knowledge.

Like it or not, any discussion directed at automation of microbiological analyses must be based on the definition of a bacterium, a definition which is obviously *not* available. Nevertheless, the concept of "the bacterium" has been around for more than a century. But at least an interpretation of what the medically oriented microbiologist means when he speaks of a bacterium, can be proffered, keeping in mind the very appropriate question asked by Alice of Humpty Dumpty (Lewis Carroll) in *Through the Looking Glass.* Humpty had said: "When I use a word . . . it means just what I choose it to mean—neither more nor less." "The question is," said Alice, "whether you can make words mean so many different things." Obviously, a bacterium is a microorganism. A microorganism is one of several types of microscopic organisms, organisms of a size requiring considerable magnification, oftentimes to the very limits of light microscope resolution, to be discerned. This physical limitation is, however, not a very good character and as biologists we must characterize microorganisms, or preferably 'protista,' as acellular organisms, organisms which carry on all the functions associated with life within the confines of a cell. It is even better to state that protista do not relegate any function to specialized cells organized into tissues; that in protista the full potential of protoplasm to carry out all required functions of a total organism can be compressed within the stricture called for lack of a better word—a cell. But a cell to the microbiologist must mean that the Lwoffian interpretation of a total organism pertains. Lwoff (2) recognized that Kluyver's (3) concept of the unity of biochemistry could be expanded into a common Biological Order based on: 1) unity of plan represented by a nucleus embedded in protoplasm; 2) unity of function stating that metabolism is essentially the same in each cell; and 3) unity of composition recognizing that the main macromolecules of all life forms are composed of the same small molecules. This basic Lwoffian order forms the theme upon which diversity of structures and functions, heredity, speciation and groupings have found the multiple expressions extant in nature. It is this Lwoffian concept of biologic unity which threads together all living forms including the microbial world. Bacteria are thus at the very level of imposing order on organic molecules of possibly prebiologic origin. They represent along with the blue-green algae or myxophytes the most primitive level of organismal organization described by Chatton as a procaryotic. Most biologists and certainly other scientists ignore the far-reaching differences which separate procaryotes from eucaryotes. There are some differences of obvious consequence in assessing bacterial responses and patterns for their recognition. Thus, the communication between DNA and the cytoplasmic machinery is more direct in the procaryotic forms. This implies that the interplay between changes in either major compartment, i.e., heredity or environment, can be expressed immediately and without the refinements or controls exercised by zygote formation and complex cytoplasmic organelles. However, this primitive or archaic organization prevents the recapture of evolutionary trends which have led to the present, artificial groupings of bacteria. While certain phylogenetic interfaces may become established, the ontogeny of a bacterium is totally obscured. At this juncture there is a great temptation to cite such important modifying factors as plasmids and episomes. Instead, one must admit the collective ignorance which attends the subcellular anatomy of both pro- and eucaryotic organisms—an ignorance which does not permit recognition of the individual in the large population of similar forms and emphasizes that morphology cannot be the sole criterion for classification of microorganisms. As applied to bacteria, our limitations in recognizing an individual appear unsurmountable from the biologic viewpoint. There are several additional factors which bear on this point. The modalities which serve microbiologists today do not answer readily the question: Is this individual organism alive or dead? Of course, there are some physiologic measurements which could be applied to microorganisms domesticated in the laboratory, but their diagnostic value is quite minimal when applied to natural specimens including those of clinical origin. The only generally acceptable indicator of microbial life is the proliferative activity of protista in artificial media, in many instances by artificial separation of mixed populations into pure culture components. This identification by growth and separation is aided and abetted by the introduction of enrichment technique designed to suppress a segment of the microbial particles of a given sample while encouraging the growth of another; in other words, the technique converts a minority into a majority population by artificial means. Unfortunately, the artificially imposed enrichment is assisted quite frequently by inadvertent exclusions of the majority of microbial inhabitants in a given sample. For instance, the overwhelming microbiota of a fecal sample require anaerobic conditions, a fact ignored completely in the clinical situation. This has led an appreciable number of laboratory scientists and their clinician colleagues to regard the family Enterobacteriaceae and some streptococci as the major normal microbial residents of the lower GI tract. The interplay between the host and the remaining anaerobic residents has been disregarded almost completely until recently. It may well be, unlikely as it seems, that the vast residuum of intestinal anaerobes need not be considered in the definition of host pathology. These protista cannot be ignored in the definition of the host's health, especially not since this vast reservoir of microorganisms represents a series of ecologic sequences. Shifts in the ecologic arrangement produced unintentionally as by the addition of antimicrobial agents lead to changes which must and do affect the wellbeing of the host. We accept that the collection of organisms we designate by a generic and species appellation constitutes a related pool of distinct individuals which share certain biochemical and physiological activities but which can be divided further on the basis of antigenic constitution and virus susceptibility. Admittedly, molecular biology has provided additional tools as yet unapplied to clinical and most other branches of microbiology. I must confess that I have been plagued most of my professional life with a question I have been unable to resolve. In its simplest form my doubt may be stated as follows: Is the microorganism we grow under admittedly artificial conditions in the laboratory identical to the microorganism that exists under natural conditions? Are the attributes so significant in taxonomy or diagnosis expressed by the organism during its tenure in the host? Are we in our collective preoccupation to label and categorize looking in reality at a variant of a large population selected especially by the conditions we provide in the petri dish or test tube while the host environment tends to select another group of variants particularly suited for survival under these conditions? I might even go so far as to inquire if there can be a difference between the microorganisms which leads a commensal or saprophytic existence in an equilibrium state with a host and the microorganism which will become involved in the complication of a disease process, ignoring at this time the primary or secondary degree of causality? In other words, can amphibiosis encompass various population potentials which are selected by the conditions reflecting change in the host or other environments? This quest can be extended to the next level. We know that even in pure culture the very activity we call growth is accompanied by environmental changes we can observe readily in a closed system such as in a measured volume. Are the microorganisms present at the initiation of multiplication completely identical in every respect with those during the exponential growth phase or those which still can proliferate during the declining stages of the stationary phase. Some of the facts unraveled by molecular biologists indicate that various feedback mechanisms control enzyme synthesis in protista. Continued growth in an exhausted medium must therefore, require an altered constitution. This alone would suggest an ordered sequence of different groups which we recognize as but one population. The experience of the clinical microbiologist suggests many other manifestations of this consideration. The selective capacity of the skin for certain specific microorganisms, the rarity with which Staphylococcus aureus participates in disease of the outer nares and its environs, the differences between Escherichia coli in the intestinal tract as compared to its role in bacteriuria are but a few examples of the observations we have recognized but not explained adequately at the microbial level.

Antibiotic therapy and antibiotic addition to commercial products have revealed further aspects of this fundamental problem. We have seen in the laboratory and under pathologic conditions the phenomenon of the persistor organism. It is a bacterium quite alive but not multiplying at the time an adequate quantity of an antimicrobial agent is in its intimate environment, an antimicrobial agent demonstrably effective against the persisting organism once it can be induced to grow. Here we have an excellent example of microbial life without the display of proliferative activity. Just what causes this prolonged lag phase in the persisting bacterium in the laboratory is not known. Equally unexplored is the tissue persistor, although the possibility of intracellular existence possibly as an L-form has not been ruled out. Antimicrobial agents have emphasized the role of extrachromosomal DNA plasmids as interbacterial purveyors of unstable genetic information as well. We accept the role of plasmids and episomes vis-a-vis the antimicrobial drugs but ignore largely the effect other interbacterial communications could have on such populations. We do know that intraspecies discrimination can be exercised by certain variants by the production of bacteriocins while bacteriophages, temperate in some members of a so-called species, can be quite virulent for others. What emerges from these considerations of pure culture ecology is a very complex array of factors. Work performed in my laboratory many years ago covering the establishment of Candida albicans as a member of the intestinal microbiota suggests a far greater complexity when a multicomponent biosystem is studied (4). The fact that any subspecies category of microorganisms must confront the sum total of all of the given reactions not only of its close relatives but of all the components of a very dynamic, interacting ecologic system multiplies these complex interactions many times and is perhaps the best reason why pure culture studies have survived for so long.

It seems logical to consider next our knowledge concerning microbial species. After all, the object of the exercise of characterizing bacteria is to call them by name which means of course by their genus and species designation. Much has been written and said about species in general and about bacterial species specifically. In his trenchant essay "The Microbial Species—A Macromyth?" S. T. Cowan (5) describes the folly of classifying bacteria according to the rules governing groups which reproduce sexually. While it can be argued that the concept of species is desirable the actuality of bacterial species cannot be achieved. Bacteria, as has been pointed out already, interact continuously with their environment and each other in a continuous process of evolution, made possible by their haploid as well as procaryotic state. While we can catalogue the physiologic, biochemical, immunologic, and phage susceptibility characteristics of a population, we cannot achieve this end with the individual bacterium. In addition, we can but list a number of selected characters of this population. In this manner, we may characterize or diagnose a bacterial population identified earlier by the same set of selected characters. Classification on the other hand requires comparison of a large number of characters of equal weight. Even the type concept falls under the weight of bacterial illiteracy, for intermediate forms abound without allowing for the clearcut breaking points to separate these units. In addition, interspecies and intrageneric matings have been achieved in the laboratories of Zinder (6), Baron and coworkers (7), Luria and Burrows (8) to name but a few of the early investigators. But as practical scientists, we must have a system of units to which we can attach names, states Cowan, not as an exercise in nomenclature but for the purpose of identification. Without getting sidetracked by the various quasi-legalistic arguments and considerations which amuse taxonomists, I find the approach originally suggested by Edwards and Ewing (9) for the family Enterobacteriaceae a satisfactory starting point for the identification or diagnosis of medically significant bacteria. Undoubtedly, the simplifications I have introduced will not meet with the approval of purists or even tolerant taxonomists. They are the interpretations of a simple clinical microbiologist attempting to explain the dynamic state of microbial identifications in the medical laboratory. We can regard the family Enterobacteriaceae or any other so-called family as an enormous mass of individuals or bacterial populations. Within this mass there are certain denser areas occupied by those microorganisms which share a number of biochemical, physiologic, antigenic, and phage properties. The dense population centers, these "identification urban areas" change gradually through a "suburban landscape" of lesser density to a "country-like setting" where the paucity of individuals is the greatest. As one approaches the vicinity of another urban center within the family area, densities increase regardless of the direction from which one arrives. This hypothesis allows for the diagnosis of species and/or genera at the dense level of occupancy, the recognition of shared characters and the biologic interaction between individuals resulting in the appearance of characteristics not associated with a particular group heretofore. Thus, without consideration of mechanism, this diagnostic scheme permits H_2S-positive Escherichia coli; H_2S-negative Citrobacter; indole-positive Enterobacter cloacae, etc. We must admit that our interest in establishing a significant interaction between a specific bacterium and a certain host tends to distort our interpretation. Thus, an organism might be disregarded in a specimen as inconsequential were it not for a peculiar biologic character which calls it to the attention of the diagnostician. Repeated isolation of such an easily discernible variant could lead to assigning to the variant greater significance than it deserves.

I think we have now arrived at the most crucial consideration confronting all innovators in the clinical microbiology area. The isolation of a bacterium from a clinical specimen is insufficient for the interpretation of its role as an actual or potential purveyor of infectious disease in a particular host. It seems almost superfluous to state that while in many instances an appreciable number of representatives of a so-called species are required for implication in a disease process, other times but a single colony augurs the diagnosis. As stated earlier, a bacterium appearing in a sample from one body area is considered a member of the host's microbiota while in another specimen it has definite pathologic implications. A specimen not obtained under stringently controlled conditions—and unfortunately few really are—may harbor the contaminants which obscure, outgrow or suppress the more significant or actual inhabitants of the pathologic site. The treatment of the location whence the specimen is obtained, its handling, transport, and laboratory evaluation contribute substantially to the interpretation of results. Even these factors are minor considerations in the absence of pertinent information about the host, the patient. Adequate interpretation of clinical microbiology findings in the absence of knowledge concerning the disease manifestations, therapy, and exposure, is not possible in today's medical facilities. In many instances pathologic specimens obtained from nonhospitalized patients suffer a similar fate. The objective of these arguments is to underline the inescapable conclusion that judgment concerning a microbial constituent in a clinical specimen cannot be made by the detection of its very presence. I do not mean to belittle or to detract from the fabulous speed and encyclopedic memory possessed by the modern computer, easily coupled to any automated device deemed applicable to the clinical microbiology situation. But the clinical microbiology laboratory itself is emerging from more than two decades of neglect, brought about by the fervent belief that antibiotics would eradicate most if not all infectious disease. The methods used were hailed as modern and advanced in the days of Pasteur and Koch; they are ancient today and do not permit in many cases the recognition of significant microbial forms which may represent stages in bacterial life cycles. The complexities of microbial ecology and host-parasite interactions are another stumbling block. Pure culture technique deprives us of recognizing concerted activities of microorganisms while our biochemical and physiologic yardsticks are inadequate. Perhaps the greatest disappointment which confronts the nonbiologist is the realization that even the nutrient environment we provide for the isolation, characterization, recognition and maintenance of our test objects has not been standardized to the point where we can insure reproducibility of conditions. During the era of interest in vitamins, essential amino acids and mineral nutrition, minimal growth requirements were defined for a number of microbial organisms. The concept of complete chemical definition for optimal cell yields of microbial populations has never gained popularity. The very nature of the mostly agamic haploid procaryotes has prevented evaluation of substrate, mineral environment, osmolarity, atmosphere, pH, redox changes, etc. in all but a very select number. This lack of information extends to the reaction of pure cultures to inhibitory agents such as disinfectants and antibiotics. The differences in susceptibility of the same population to the same amount of the same chemical agent at different age levels with different nutrient supplements and with slight changes in temperature and other physical factors is accepted and artificially controlled by microbiologists. The conclusions are applied to natural situations which may not mimic the laboratory conditions.

This recital of unknown, unexplored facets of microbiology which could be continued is not an indictment of microbiologists. Many of the questions raised here are outside our ken because the biologist's advances are intimately intertwined with the growing understanding of Nature by the physical sciences.

References

1. Stanier, R. Y. and van Niel, C. B. The Concept of a Bacterium, Arch f Mikrobiol 42:17–35, 1962.
2. Lwoff, A.: *Biological Order*. The M.I.T. Press. Cambridge, Ma., 1962.

3. Kluyver, A. J.: *The Chemical Activities of Microorganisms.* University of London Press. London 1931.
4. Isenberg, H. D., Carito, S. Pisano, M. A. and Berkman, J. I.: Factors Leading to Overt Monilial Disease. I. Preliminary Studies of the Ecological Relationship between Candida albicans and Intestinal Bacteria, Antibiotics and Chemotherapy 10:353–363, 1960.
5. Cowan, S. T.: The Microbial Species—A Macromyth, Symp Soc Gen Microbiol 12:433–455, 1962.
6. Zinder, N. D.: Hybrids of Escherichia and Salmonella, Science 131:813, 1960.
7. Baron, L. S., Spilman, W. M. and Carey, W. F.: Diploid heterozygous hybrids from matings between Escherichia coli and Salmonella typhosa, J Exptl Med 112:361–364, 1960.
8. Luria, S. E. and Burrows, J. W.: Hybridization between Escherichia coli and Shigella, J Bact 74:461–465, 1957.
9. Edwards, P. R. and Ewing, W. H.: *Identification of Enterobacteriaceae.* 1st Edition. Burgess Publishing Co. Minneapolis, Mn. 1955.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 1, JANUARY–FEBRUARY, 1977
Printed in U.S.A.

Proficiency Testing in Clinical Microbiology: The New York City Program*

MARION E. WILSON, PH.D., YVONNE C. FAUR, M.D., S. SCHAEFLER, PH.D.,
IRENE WEITZMAN, PH.D., MARTIN H. WEISBURD, M.S., AND
MORRIS SCHAEFFER, PH.D., M.D.**

Abstract

A program of proficiency testing and laboratory improvement in several major aspects of clinical microbiology has been developed by the Public Health Laboratory Services of The City of New York, Department of Health. The history of this development from the early 1960's is reviewed, and the methodology of evaluating the performance of clinical laboratories in diagnostic bacteriology, antibiotic susceptibility testing, mycology, and mycobacteriology is described. The value of proficiency testing, together with workshops and field consultations, as a means of applying external quality control, is demonstrated with data reflecting improved laboratory standards and practice over the past decade. One of the most valuable though undocumented effects of the program has been an increasingly productive interchange between our laboratories and those of participants.

INTRODUCTION

In the early 1960's, surveys conducted in New York City revealed widespread poor performance in diagnostic bacteriology as practiced in many clinical laboratories (1). Subsequently, concerted programs for proficiency testing and clinical laboratory improvement were developed by the Public Health Laboratory Services of the City of New York Department of Health. A two-phase study was conducted to measure objectively the level of competence of clinical laboratories operating under the provisions of the New York City Health Code (phase I), and to determine the efficacy of retraining programs designed to improve performance (phase II), (2, 3).

The results of phase I indicated that about 40% of all hospital laboratories and about 50% of independent laboratories performed unsatisfactorily when tested for proficiency with unknown samples simulating clinical specimens with a mixed bacterial flora. Analysis of the laboratories with respect to their organization and technical competence indicated that consistently satisfactory performance was directly linked to the employment of full-time competent supervisors, including Directors of Microbiology in immediate charge of the work. Laboratories with a very small work load, and hence inadequate experience in microbiology, also performed poorly as a rule (2).

From The City of New York, Department of Health, Bureau of Laboratories, New York, N.Y. 10016.

Requests for reprints should be sent to: Dr. Marion E. Wilson, Public Health Laboratories, Room 201, 455 First Avenue, New York, N. Y. 10016.

* Supported by Grant #5 R 18 HS 00072-03 HSDG National Center for Health Services, Res. & Dev. HSMHA, PHS, DHEW.

** Currently, Bureau of Biologics, FDA, Bethesda, Md. 20014.

In phase II, training programs involving workshops and field consultations demonstrably effected some improvement in consistently poor laboratories participating in bacteriology. However, overall analysis of results indicated that improvement could also be attributed to repeated proficiency testing itself, as well as to the insistence with which minimum standards were presented and enforced (3).

Since that time the program of performance surveillance has been expanded to include a number of areas in microbiology in addition to general bacteriology. Antibiotic susceptibility testing has been under study since 1972. Difficulties in evaluating performance in this area have been related to a general lack of standardization of methodology in clinical laboratories. A method for approaching this problem will be described. Proficiency testing in mycology was begun in the first half of 1971, and mycobacteriology was introduced in the spring of 1974. In antibiotic susceptibility testing and mycology, the accumulating evidence supports our previous observations in bacteriology that the performance test, as a method of applying external quality control, promotes an improvement in proficiency over a period of time, probably because it repeatedly stimulates laboratories to reexamine the level of standards being maintained. This effect is enlarged if the testing is followed and supported by educational programs such as workshops, consultations, or simply well-designed critical analyses of the proficiency test results. The data for mycobacteriology are as yet insufficient for similar comment.

This paper describes our four proficiency programs in microbiology as we are currently conducting them, i.e., bacteriology, antibiotic susceptibility testing, mycology, and mycobacteriology. Each is presented as a separate entity, with a description of methods for preparation and distribution of specimens, scoring, evaluation of results, and a discussion of the particular approaches to each discipline. A section of general discussion then follows.

BACTERIOLOGY 1964–1974

Materials and Methods

During the last ten years each laboratory in New York City holding a permit in bacteriology was issued two simulated specimens on each of four occasions per year. Every specimen contained a minimum of two or a maximum of three different organisms selected to represent indigenous bacterial flora as well as pathogenic bacterial species most frequently encountered in that type of specimen. Each test series thus consisted of two specimens per laboratory, containing a total of 4 to 6 bacterial species.

Test samples were prepared to simulate various clinical materials such as sputums, urines, stools, wounds, or other specimens that commonly display a mixed flora. Test laboratories were asked to isolate and identify all organisms, pathogenic or nonpathogenic, and to report their results by mail within 7 days.

Bacterial Strains: The organisms used were either stock strains from the

New York City Department of Health collection or type collection strains. Selected organisms were held in a frozen state at −70°C and tested periodically for purity, colony morphology, biochemical and serological properties. Only colonies of characteristic biotypes were maintained for use in proficiency testing specimens.

Table I lists some of the strains that have been used most frequently in these specimens. It should be noted that these organisms represent either the majority of isolates commonly reported by diagnostic laboratories from their total workload, or less frequently encountered pathogens of major import.

Specimen Preparation: Each simulated specimen was first pretested experimentally to determine the proper concentration of each organism to be used in the mixture. Particular attention was focused on the possibility of antagonistic interactions which can affect the viability of organisms and alter the proportions of organisms as they grow out in subculture of the specimen. Organisms must remain viable in the mixtures for a minimum of 10 days, to cover the time required for delivery of proficiency test specimens to participating laboratories.

The two or three organisms selected for the mixture were subcultured from the frozen state onto blood-agar plates and controlled for morphological, biochemical, and serological properties. A twenty-hour nutrient agar culture from each organism was then suspended in 10 ml of a 0.3% sterile gelatin solution and the relative concentration of the pure suspensions was determined by nephelometry.

Mixed samples were prepared by adding appropriate amounts of each pure suspension of organisms to 150 ml of a 0.3% gelatin solution. The specimen was gently mixed on a magnetic stirrer for 10 minutes at room temperature in order to obtain a uniform distribution of organisms. When fastidious organisms such as streptococci, Shigella, or Clostridia were used, sterile defibrinated sheep blood was added to give a final concentration of 1%, in order to assure prolonged viability.

Tests were made of control samples from the mixtures on the day of preparation. Controls included transfers to appropriate selective, differential, and enriched plated media. After 20 hours of incubation these plates were assessed for typical colonial morphology of each organism in mixed growth and for the relative numbers of each bacterial strain included. If any organism grew too sparsely, the mixed suspension could be adjusted at this point by adding more of the pure suspension of the strain in question.

Similar controls were made during a ten day period of storage of the mixtures at 4°C to ascertain whether the original proportion of organisms held steady. Organisms were re-isolated from mixtures and tested periodically during the ten-day period for their biochemical and serological properties.

The specimens to be used for proficiency testing were prepared in the same manner, using the strains and the proportions of organisms found satisfactory in pretested specimens. Mixtures of suspensions were plated the day of preparation and observed after 20 hours of incubation for viability, characteristic morphology, and relative numbers.

TABLE I

Some Organisms Most Frequently Included in Proficiency Test Specimens

Gram-positive cocci	Beta hemolytic streptococci, Gr A, B, and C Group D streptococci (enterococci) Streptococcus pneumoniae Alpha hemolytic streptococci Staphylococcus aureus, coagulase positive Staphylococcus epidermidis
Enterobacteriaceae	Escherichia coli Enteropathogenic E. coli Salmonella species (except S. typhi) of different groups Arizona Citrobacter species Shigella species Klebsiella—Enterobacter—Serratia species Proteus—Providencia species
Gram-negative fermenters, non-Enterobacteriaceae	Aeromonas hydrophila
Non-fermentative Gram-negative rods	Pseudomonas aeruginosa Pseudomonas maltophilia Acinetobacter calcoaceticus (var. anitratus) Acinetobacter calcoaceticus (var. lwoffi) Moraxella species Flavobacterium species Alcaligenes species
Gram-positive bacilli	Corynebacterium diphtheriae, nontoxigenic Cornyebacterium pseudodiphtheriticum Listeria monocytogenes
Anaerobes	Clostridium perfringens Clostridium histolyticum Clostridium bifermentans Bacteroides fragilis

Suspensions were gently mixed on a magnetic stirrer and distributed in 1 ml aliquots in sterile screw cap tubes which were subsequently sealed. The prepared samples were kept refrigerated at 4°C until their delivery to test laboratories.

Samples of specimens were plated out daily during the week they were delivered to the participating laboratories and examined again for numbers, morphology, and purity. Cultures obtained from pure colonies were tested for biochemical and serologic properties to assure the validity of the proficiency test samples.

Delivery of Performance Tests: The specimens were hand-delivered within a week by Health Department examiners. Upon arrival at the participating laboratories, the examiners presented two numbered specimens, coded for each laboratory, and a report form. Seals were broken and isolation procedures initiated in the examiner's presence. The original specimen tubes were removed by examiners and subsequently destroyed. When time and staff permitted, this initial visit was followed by a return inspection, two or three days later, to observe the progress of the cultures.

Reference Laboratories: Three to five reference laboratories, chosen on the basis of reputation and continuing excellence of performance, participated in each weekly series. Each received a pair of specimens obtained from the same mixture as that distributed to all participating laboratories in the same series. Delivery to reference laboratories was always made on the last day of the series to establish continuing viability of the organisms. Final determination of the validity of the specimens was based on agreement between the reference laboratories and our own laboratory results.

Evaluation of Performance Tests: Reports from tested laboratories were evaluated with respect to success or failure in achieving essential agreement with the Department of Health and reference laboratories as to the number and identity of organisms submitted. Substantiation of identification by an adequate reported methodology was required, but due consideration was given to different approaches and procedures for isolation or identification. For organisms of controversial nomenclature, the emphasis of the evaluation was on the adequacy of reported biochemical properties rather than the semantics of designation.

Laboratories were rated for each test series (2 specimens and a total of 4, 5, or 6 organisms) as follows:

Excellent (A): at least $3/4$, $4/5$, or $5/6$ organisms, correctly identified, and all pathogens reported.

Satisfactory (B): at least $2/4$, $3/5$, or $3/6$ organisms, correctly identified, and all pathogens reported.

Unsatisfactory (C): less than half of the organisms submitted were correctly identified, pathogens were incorrectly reported, missed, or not substantiated, or no agreement existed between the test laboratory results and those of the reference and Department laboratories.

Results

Proficiency test results from 1964 to 1974 are presented in Table II. Laboratories are grouped in four categories: those in voluntary, proprietary, and municipal hospitals, and independent laboratories. The table summarizes the first 2 years' and each succeeding year's levels of achievement for these categories by grade (A = Excellent, B = Satisfactory, C = Unsatisfactory).

When A and B ratings are considered together as representing acceptable performance, and C ratings are viewed separately, it can be seen from Table II that performance has improved markedly over the years. At the program's inception, in the years 1964–1966, 46% of all labs failed to perform satisfactorily, but there has been a continuous decrease in the overall percentage of C ratings to 8.8% in 1973, and 10.3% in 1974.

There were fluctuations in the failure rate for different categories of

TABLE II

Proficiency Evaluations in Clinical Bacteriology 1964–1974

	Type of Laboratory	A*		B*		C*		Total Test No.
		No.	%	No.	%	No.	%	
1964–1966	Voluntary	63	30	52	25	94	45	209
	Proprietary	37	25	36	25	73	50	146
	Municipal	27	64	11	26	4	10	42
	Independent	63	25	62	25	125	50	250
	Totals	190	29	161	25	296	46	647
1966–1967	Voluntary	32	34	38	40	25	26	95
	Proprietary	21	29	24	32	29	39	74
	Municipal	10	62	4	25	2	13	16
	Independent	43	34	35	27	49	39	127
	Totals	106	34	101	32	105	34	312
1967–1968	Voluntary	75	47	45	28	41	25	161
	Proprietary	22	35.4	18	29	22	35.4	62
	Municipal	16	70	7	30	0	0	23
	Independent	72	42	54	32	45	26	171
	Totals	185	44	124	30	108	26	417
1968–1969	Voluntary	103	47	86	40	28	13	217
	Proprietary	27	35	36	48	13	17	76
	Municipal	30	61	17	35	2	4	49
	Independent	74	38	79	41	40	21	193
	Totals	234	43	218	41	83	16	535
1969–1970	Voluntary	164	53.0	100	32.2	45	14.5	309
	Proprietary	43	41.3	38	36.5	23	22.1	104
	Municipal	51	67.1	21	27.6	4	5.3	76
	Independent	80	30.7	118	45.3	62	23.8	260
	Totals	338	45.1	277	37.0	134	17.8	749
1970–1971	Voluntary	212	69.0	67	21.8	28	9.1	307
	Proprietary	67	61.4	26	23.8	16	14.6	109
	Municipal	60	79	14	18.4	2	2.6	76
	Independent	116	47.3	86	35.1	43	17.5	245
	Totals	455	61.7	193	26.1	89	11.9	737
1971–1972	Voluntary	175	59.0	99	33	24	8	298
	Proprietary	47	47.4	39	39.4	13	13.1	99
	Municipal	57	76	17	22.6	1	1.3	75
	Independent	89	35.4	125	50	37	14.6	251
	Totals	368	50.6	280	38.7	75	10.3	723
1972–1973	Voluntary	135	57.4	84	35.7	16	6.9	235
	Proprietary	33	42.8	37	48.0	7	9.0	77
	Municipal	50	83.3	10	16.7	0	0	60
	Independent	60	35.5	84	49.7	25	14.7	169
	Totals	278	51.3	215	39.7	48	8.9	541
1973–1974	Voluntary	117	55.5	76	36.0	18	8.5	211
	Proprietary	32	42.1	36	47.4	8	10.5	76
	Municipal	47	78.3	11	18.3	2	3.3	60
	Independent	75	41.7	78	43.3	26	14.4	179
	Totals	271	51.4	201	38.1	54	10.3	526

* A = Excellent, B = Satisfactory, C = Unsatisfactory.

laboratories, but these can probably be attributed primarily to the continuous turnover in technical and supervisory personnel that occurs in clinical laboratories.† The overall view is one of solid improvement of laboratory performance in clinical bacteriology, with more than half (51.4%) of all laboratories now achieving excellence as compared with 29% performing at that level in 1964–1966.

Discussion

The method used for the preparation, evaluation, and control of bacteriological specimens included in the New York City proficiency testing program has proved to be reliable and reproducible, and has enabled us to evaluate the general level of competence of laboratories in isolating pathogenic organisms from mixed cultures and in making final identifications with relevant accuracy.

The bacterial strains used were selected to represent those most frequently encountered in clinical situations, and the choice was often guided by current epidemiological information. In recent years, for example, a greater emphasis was placed on evaluating procedures for the isolation and identification of anaerobes.

Continuous evaluation of laboratory performance provides a reasonable measure of the level of competence of individual laboratories and recognition of the consistence with which standards are maintained. The number of laboratories that consistently perform poorly has decreased steadily over the years since our program was initiated, for a number of reasons. There is evidence to indicate that frequently repeated proficiency testing, coupled with repeated inspections that provide guidance toward and enforce minimum standards for facilities, staff, and technical procedures are responsible for this improvement to some degree (3).

In addition, several series of workshops and a field consultation program were instituted in a concerted effort to assist those laboratories that were consistently poor. Workshops consisted of several series of lectures and laboratory sessions, each given over a 12–14 week period. They covered the major aspects of clinical bacteriology, emphasizing an ordered approach to rapid isolation and accurate identification of pathogenic bacteria of greatest clinical importance. A manual of procedures was developed and distributed to workshop participants for their permanent use. Its contents included guidelines for quality control, as well as discussion of the basic principles of techniques.

At the same time, a group of expert clinical microbiologists was assigned to provide consultation to laboratories that frequently reported unsatisfactory results in proficiency test series. Each laboratory was visited by a consultant three times at monthly intervals, but continuous contact with laboratories was maintained for much longer periods of time.

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† Detailed analysis of the problems exhibited in Table II were presented in earlier publications (2, 3).

As described previously (3), in following the subsequent performances of laboratories that had participated in the workshop and consultation programs, it was apparent that their overall record in proficiency tests issued subsequent to instruction was distinctly improved when compared with the continuing record of poor laboratories that had not been included in this study. Furthermore, these instructional efforts had the salutary effect of pressing home to participants from laboratories with a very small work-load in bacteriology that it is impractical, if not impossible, to maintain quality control and technical standards under such circumstances, and a number of these subsequently withdrew or relinquished their permits to operate in this area.

It should also be noted that the workshop and consultation programs were continued through a three year period, from 1969 to 1972, during which time comparisons were made of the effect on reported proficiency tests of varying the method of delivering specimens, that is, by mail, messenger, or examiner-observer. The results of the study reinforced our original experience that for bacteriologic specimens, which require several days for work-up and completion, it makes little difference how the laboratory receives them. Reported results were good or bad along the usual lines of competence (or through referral to a consultant). In other disciplines, such as clinical chemistry, an examiner who delivered specimens could observe the entire procedure by which results were obtained, and his presence did make a difference when such results were compared with those reported for mailed or dropped-off specimens. In the latter two instances, results were consistently better for many laboratories. In bacteriology, however, an examiner could at best observe the initial handling and subculture of the specimens, but could not routinely follow up the work over ensuing days (4).

Further comments on factors common to this and the other programs to be described are made in the General Discussion.

ANTIBIOTIC SUSCEPTIBILITY TESTING

Evaluation of the proficiency of clinical microbiology laboratories in New York City in performing antibiotic susceptibility testing was begun in the fall of 1972. The goal of the program was to assess the routine performance of participating laboratories in providing adequate reports of the antibiotic susceptibility of commonly encountered bacterial pathogens, and to contribute to the standardization of methodology in clinical laboratories.

Materials and Methods

Bacterial Strains: Two of the organisms included in proficiency test specimens for bacteriologic work-up were designated for evaluation of proficiency in antibiotic susceptibility testing. The mode of delivery of the specimens and the selection of the reference laboratories were the same as described for proficiency testing in bacteriology. Rapid-growing aerobic or facultative anaerobic organisms were selected to represent either standard sensitive strains used for quality control in antibiotic susceptibility testing, or organisms resistant to one or several antibiotics, with special emphasis on multiply-resistant strains associated with hospital infections.

The organisms selected for testing were: Escherichia coli, Enterobacter, Klebsiella, Proteus morganii, Providencia stuartii, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, and Streptococcus viridans. Included in the group were methicillin resistant strains of S. aureus and S. epidermidis and gentamicin resistant strains of Proteus morganii, Providencia stuartii, and Pseudomonas aeruginosa. The standard strains E. coli ATTC 25922 and S. aureus 25923 were submitted at the beginning of the program, and at one later date, to provide comparative data on the level of quality control among participating laboratories.

Antibiotics: A comparative evaluation of clinical laboratories is often difficult because of wide variations in the spectrum of antibiotics used by different laboratories. For this reason, a method was devised to allow comparative numerical evaluation and at the same time to reflect the actual spectrum used by each participating laboratory. The antibiotics to be tested were divided into two groups: 1) those required for testing (ampicillin, cephalothin, chloramphenicol, gentamicin, kanamycin, penicillin, and tetracycline), and 2) optional antibiotics, or any others which would normally be used by the participating laboratory to test the organism in question.

The results obtained with the required antibiotics permit a comparative evaluation of different laboratories, while the data for optional antibiotics provide information on whether different spectra are used for Gram-positive and Gram-negative organisms, as well as on the specific choice of certain antibiotics, as for example penicillinase-resistant penicillins for Staphylococcus or carbenicillin for Pseudomonas aeruginosa.

Techniques: There can be marked differences in the results of in vitro antibiotic susceptibility testing traceable to the culture medium, inoculum, pH, and other factors, and although the classification of an organism's susceptibility to a given antibiotic as "sensitive," "intermediate," or "resistant" is of great practical value, the boundaries of these interpretations are sometimes ill defined. For this reason, a standardized method for antibiotic susceptibility testing was recommended by the Report of an International Collaborative Study on Antibiotic Susceptibility Testing (5). The standard presently recognized in the United States is the Kirby-Bauer method (6). Alternative methods used should give results comparable with those obtained by the Kirby-Bauer technique.

For our evaluation program, a check list was prepared (Table III) requesting information from each laboratory on various aspects of antibiotic susceptibility testing by the disc diffusion method such as: primary isolation, media, inoculum control, antibiotics used, and criteria of interpretation. The aim of the questionnaire was to determine whether proper methods were being used with regard to such parameters, and to assess the degree of standardization applied to antibiotic susceptibility testing by participating laboratories.

TABLE III

The City of New York—Department of Health—Laboratory Services
DIVISION OF LABORATORY IMPROVEMENT
455 First Avenue, New York, N.Y. 10016
Check List for Clinical Laboratories
ANTIBIOTIC SUSCEPTIBILITY TESTING

Date: ____________ ____________
Name of Laboratory ____________ Signature: ( ) Lab Director
Address ____________ ( ) Lab Supervisor

I. Inoculum

a. Specimen plated directly? ____________

b. Isolated colony used. Do you use a single colony? ____________
Several identical colonies? ____________ Do you suspend the colony in saline or broth and inoculate the plate? ____________
Subculture in broth? ____________ Type of broth? ____________

c. Standardization of the broth culture. No ____________ Yes ____________
The standardization is carried out by: Adjustment to barium sulfate standard ____________: adjusted photometrically ____________; by dilution, 1: ____________ of a culture of ____________ hrs.: other method of standardization, specify, ____________

II. Method of inoculating plated medium (swab, loop, pipette, glass rods etc.): ____________
____________.

Time interval and temperature *between* plating of inoculum and disc application, ____________.

III. *Nature of Media Used*

a. The basal medium used in antibiotic susceptibility testing is, ____________

b. Enrichment is added to the basal medium routinely ____________ on some occasions ____________ never ____________.
The following enrichments are used: Blood ____________ %,
human ____________, sheep ____________,
other blood ____________ whole blood ____________,
chocolate blood ____________.
Other supplements, specify, ____________.

c. Diameter of plates routinely used, ____________ mm, average volume of medium per plate ____________ ml.

d. Storage of plated medium: Room temperature, ____________ refrigerator, ____________ for how long, ____________.

IV. *Antibiotics*

a. Source, ____________

b. Age (Within expiration date?), ____________

c. Temperature of storage, ____________ Dessicator used? ____________

d. Kept at room temperature during day? ____________

e. Types of discs used: High concentration only, ____________
High and low concentration, ____________. Low concentration only, ____________
How many discs per plate? ____________ How applied to plate, ____________

f. Different batteries for different organisms? Yes ____________ No ____________
If yes, specify your routine: ____________
____
____

TABLE III—*Continued*

g. Incubation of inoculated plate *after* disc application:
Temp.____________ Time interval ____________

V. *Reading and interpretation*
a. Zone of inhibition is usually regarded as: Complete inhibition of growth,
____________________________________.
Inhibition of heavy growth, ______________.
b. Zone size measured? No________ Yes ________. Zone measurements made with ruler, ______________.
Micrometer,______________ Comparison with template, give source of template ______________Other: specify, ______________
c. Terminology and *criteria* used for reporting sensitivity, moderate (intermediate) sensitivity, and resistance, ______________________________
____

VI. *Quality control*
No________ Yes________ If yes, specify strains used in quality control, ________
____
Mode of preservation of strains______________________________
Do you have a fixed schedule of quality control? specify,______________________
Do you keep graphs or a quality control log book?______________________

VII. *Tube and plate dilution*
Do you routinely perform antibiotic susceptibility testing by tube or plate dilution? No________ Yes________. If yes, media routinely used ______________
Inoculum control by dilution, ______________ Other, specify,______________
Do you vary the inoculum to the antibiotic? Specify______________

Evaluation of Results: The susceptibility of the two organisms tested in each proficiency series against the seven required antibiotics was classified as either sensitive, intermediate, or resistant according to results obtained by our own laboratory and by at least a majority of the reference laboratories. The results of participating laboratories were graded as: A, A^-, B^+, B, B^- or C. A grade of C indicated failure, and B^- a marginal performance in need of improvement by workshops or consultation.

The grades C, B^-, and B were based exclusively on results obtained with the required antibiotics. A maximum of three erroneous results for the two organisms (susceptible instead of resistant or vice versa) were allowed for a passing grade.

Grading between B^+ and A (very good to excellent) took into account additional factors such as the results obtained with optional antibiotics, and the adequacy of the antibiotic spectrum.

Results

The results of the evaluation of 174 laboratories in the Fall of 1974 are given in Table IV.

An analysis of the results obtained with organisms used in different series of proficiency tests indicated a relatively high frequency of erroneous results with ampicillin, cephalothin, and to a lesser extent, with penicillin and tetracy-

TABLE IV

Evaluation of 174 Laboratories Participating in Testing Series M3, 1974

Grade	Rating	No. of Laboratories
A	Excellent	20
A⁻	Very Good	40
B⁺	Good	37
B	Satisfactory	48
B⁻	Marginal	27
C	Unsatisfactory	2
NE	Not Evaluated*	3

* Failed to identify organisms on the antibiotic report form.

TABLE V

Antibiotic Susceptibility Data for E. coli Fall 1974 and Fall 1972

Antibiotic	Expected Results*	Participating Laboratory Results					
		Sensitive		Intermediate		Resistant	
		1974	1972	1974	1972	1974	1972
Ampicillin	S	151	142	5	11	15	24
Cephalothin	S	148	146	9	15	12	11
Chloramphenicol	S	158	159	3	3	1	2
Gentamicin	S	165	167	2	0	0	2
Kanamycin	S	155	157	5	7	3	3
Penicillin	R	2	4	1	1	151	155
Tetracycline	S	153	158	10	13	7	5

* Results obtained by our laboratory and the majority of the reference laboratories.

cline. Table V illustrates these variations with respect to E. coli susceptibility testing on two occasions.

In other test series, gentamicin presented special difficulties to some laboratories which incorrectly interpreted results obtained for Proteus morganii and Providencia stuartii as sensitive, although both were in fact gentamicin resistant. Similarly, there were numerous problems in testing the responses of a methicillin resistant strain of Staphylococcus aureus, not only to penicillin and ampicillin (Table VI), but also to the optional penicillinase-resistant penicillins (Table VII).

Comparative data obtained from the methodology check lists submitted to participating laboratories at the start of the program in 1972 and again in 1974 are shown in Table VIII. Comparisons at this time can only be tentative because of incomplete responses from some laboratories, but an increased degree of standardization appears to be emerging. This improvement is suggested in such factors as the more extensive use of Mueller-Hinton medium in 1974 (83% versus 76% in 1972). The increased use of 150 mm diameter plates with 11 to 12 antibiotic discs (47% versus 28%), inoculum control with $BaCl_2$ (49% versus 34%), and a log book for quality control (81% versus 61%)

TABLE VI

Antibiotic Susceptibility Data for S. aureus (Fall, 1974)

Antibiotic	Expected Result*	Participating Laboratory Results		
		Sensitive	Intermediate	Resistant
Ampicillin	I, R**	52	24	97
Cephalothin	S	153	20	21
Chloramphenicol	S	160	1	1
Gentamicin	S	130	0	4
Kanamycin	R	20	0	127
Penicillin	I, R**	54	19	104
Tetracycline	R	26	7	134

* Data obtained by our laboratory and the majority of reference laboratories.

** Intermediate or Resistant considered acceptable.

TABLE VII

Methicillin, Oxacillin and Nafcillin Susceptibility of a Methicillin Resistant S. aureus Strain (Fall 1974)*

Antibiotic	Susceptible	Intermediate	Resistant
Methicillin	12	5	37
Oxacillin	8	0	43
Nafcillin	1	0	20

* 83 laboratories tested for susceptibility to at least one of these penicillinase-resistant penicillins.

appears in each case to have statistical significance.*

Discussion

The data supplied by the participating laboratories indicate that the antibiotic disc diffusion method is the routine method used by all participating laboratories. Although the majority of the laboratories adapted individual elements of the Kirby-Bauer method such as the use of only high potency discs or measurement of the zone of inhibition, only 48% controlled the inoculum with $BaCl_2$ or an equivalent photometric method. The sample is too small for an evaluation of the relationship between the use of the Kirby-Bauer method and the results of the proficiency testing. However, of the 29 laboratories rated in the fall of 1974 as C or B^- (Table IV), 14 did not measure the zone of inhibition, and 10 used 10 or more discs on 100 diameter plates. In previous series, among laboratories rated as unsatisfactory, or marginally satisfactory, there was also a more frequent lack of standardization than in each overall sample.

There appears to be a wide range in the frequency and methodology of applying quality control to antibiotic susceptibility testing among participating laboratories. The organisms used for this purpose, and methods for preserving them, also vary from one laboratory to another. For these reasons, the proficiency evaluation program will focus in the future on providing assistance with standardization and quality control. An initial summary analysis of some of the more common errors, together with a discussion of quality control and tabular data on optimal inhibition zones for the recommended standard control strains of E. coli (ATTC 25922) and S. aureus (ATTC 25923), has recently been distributed to participating laboratories.

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* Statistical analysis of these limited data indicates for Mueller-Hinton, $0.2 > p > 0.1$; for 150 mm plates with 11-12 discs, $p < 0.001$; for inoculum control with $BaCl_2$, $0.05 > p > 0.02$; and for log book with quality control, $p < 0.001$.

One of the limitations of quality control with standard susceptible organisms is that they do not always reflect the conditions encountered wih some bacteria of multiple resistance, such as Pseudomonas aeruginosa when tested with carbenicillin or gentamicin, or hetero-resistant S. aureus when tested with methicillin. Therefore, we will continue to include multiply resistant strains associated with hospital infections in our proficiency test specimens, and will stress in future critiques the technical problems encountered with each antibiotic tested against such strains.

Thus far our proficiency evaluation has been limited to antibiotic disc diffusion testing. Only fifteen laboratories have reported that they perform MIC (minimal inhibitory concentration) determinations by the tube dilution method, and to our knowledge very few laboratories determine serum levels of antibiotics or the antibiotic susceptibility of anaerobes. In the future we will offer a voluntary proficiency program for MIC and MBC (minimal bactericidal concentration) determinations. Depending on the response, this supplementary evaluation may be extended to other special techniques.

TABLE VIII

Comparative Data for Methods of Antibiotic Susceptibility Testing Reported by Participating Laboratories in 1972 and 1974

	Laboratories Reporting			
	1972		1974	
	No.	%	No.	%
Mueller-Hinton Medium	124	76	114	83
Other Media	39	24	22	17
Discs Per Plate				
100 mm diam. 4–6	7	5	4	3
100 mm diam. 6–8	36	25	16	12
100 mm diam. 9–10	22	15	11	8
100 mm diam. over 10	24	16	18	14
150 mm diam. 8–10	15	10	21	16
150 mm diam. 11–12	41	28	63	47
150 mm diam. over 12	1	0.6	0	
Zone measured	104		94	
Zone measured inoculum control with $BaCl_2$ standard	55	34	68	49
Zone measured other method of standardization	28	17	12	9
Zone measured no inoculum control	21	13	14	10
Zone not measured	59	36	45	32
Quality control with Log Book	93	61	111	81
Quality control without Log Book	24	16	10	7
No quality control	34	23	16	12

MYCOLOGY

The mycology proficiency program was initiated in March of 1971 when 5 fungus cultures on Sabouraud dextrose agar were distributed to 96 laboratories in the City of New York with a permit in mycology.

Materials and Methods

Specimen Preparation and Distribution: Cultures used for proficiency testing were obtained primarily from the Center for Disease Control in Georgia, the New York State Mycology Laboratory in Albany, the Mycology Laboratory at the College of Physicians & Surgeons in New York City, and from clinical specimens received for culture by our laboratory. The stock cultures were maintained in the freezer at −20°C and also on agar slants, covered with mineral oil and kept in the refrigerator at 4°C.

The specimens delivered to participating laboratories have been mature, pure cultures on agar slants in screw-capped test tubes. Each shipment of specimens is accompanied by an instruction sheet (which included a 6-week due date for results, as well as information about each specimen, such as a hypothetical source, tentative diagnosis, and the level of identification required, i.e., genus only or genus and species), and a separate report form for each specimen where information regarding the microscopic and macroscopic morphology, biochemical and physiological tests, and final identification are to be recorded.

Initially the goal was to distribute 5 specimens four times a year, but because of limitations in field staff for distribution of proficiency tests, the program was changed in late 1973 to match the pattern of the New York State program in mycology, i.e., ten specimens twice a year. To be eligible to receive these specimens and maintain their permits, all laboratories participating in the mycology proficiency testing program must also be equipped with an adequate Biological Safety Cabinet. This requirement became effective as of January, 1973 to comply with standards set by the Clinical Laboratory Improvement Act of 1967 for laboratories engaged in interstate commerce.

Determination of Validity of Specimens: Prior to inoculation for distribution to participants, each culture chosen for a proficiency testing series is checked for characteristic morphology (microscopic and macroscopic), biochemical and physiological properties, and stability during a 3-week refrigeration period.

A specimen was considered valid if at least a majority or more of the reference laboratories, including our own, agreed on the results. On occasion, some reference laboratories reported variant results and were asked to recheck their observations or perform additional tests. If agreement on identification was then reached, the specimen was considered valid; otherwise, it was ruled atypical and disqualified.

Early in the program the reference laboratories were chosen from those specializing in mycology. This policy was later expanded to include some participating laboratories that consistently performed well during the course of the program.

System of Grading: The passing grade for each proficiency test series is currently 70%, approximating the standard of the New York State program in mycology (7). An example of point assignment in a 5-specimen series with 2 sets of different organisms for distribution is shown in Table IX, where fully correct identifications are awarded 20 points per organism. In a 10-specimen series, each correct identification is awarded 10 points. The assignment of partial credit depends on the seriousness of errors. Little or no credit is won if a saprophyte is reported rather than a pathogen, or vice versa, even though the genus is reported correctly (e.g., Cryptococcus albidus for C. neoformans, or vice versa).

In the earlier phases of the mycology program, the passing grade for a series was based on the lowest mark achieved by the top ten (referees) of the participating laboratories (4), but when this grade dropped to a low of 50% in one series the more stringent standard described above was adopted.

Results

The results of the proficiency testing program in mycology for the two-year period from 1972 to early 1974 are presented in Table X. The first series, 71-MYC-12, is not included because no passing grade was assigned to this trial series. Beginning with series, 72-MYC-20, two sets of specimens, a single letter set and a double letter set, were distributed to participating laboratories. Each set was distributed equally among participating and reference laboratories. In

TABLE IX

Point Assignment in a 5-Specimen Series With 2 Sets of Organisms

Single Letter Series A–E		Double Letter Series AA–EE	
A. Cladosporium sp.	20 points	AA. Cladosporium carrionii	20 points
Hormodendrum sp.	20 points	Cladosporium sp.	5 points
		Hormodendrum sp.	5 points
B. Fusarium sp.	20 points	BB. Trichophyton rubrum	20 points
		Trichophyton	10 points
C. Candida guilliermondi	20 points	CC. Candida parapsilosis	20 points
Candida sp.	10 points	Candida parakrusei	20 points
		Candida	10 points
D. Geotrichum candidum	20 points	DD. Trichosporon cutaneum	20 points
Geotrichum sp.	20 points	Trichosporon sp.	20 points
E. Allescheria boydii	20 points	EE. Eurotium	20 points
Monosporium apiosperum	20 points	Aspergillus glaucus group or member of this group	20 points
		Aspergillus	20 points
		Aspergillus (incorrect group reported) but not fumigatus	18 points
		Aspergillus fumigatus group	10 points

Minimum passing grade—70%.

TABLE X

Results of Proficiency Testing in Mycology from 1972 to 1974

Series	72-MYC-20	72-MYC-48	73-MYC-18	73-MYC-50	74-MYC-16
No. of specimens	5	5	5	10	10
Evaluated reports	90	86	44	53	57
No. passed					
pg* 70% A–E	28 (62%)	64 (74%)	32 (73%)	46 (87%)	52 (91%)
50% AA–EE	32 (71%)				
No. Unsatisfactory					
A–E	17 (38%)	22 (26%)	12 (27%)	7 (13%)	5 (9%)
AA–EE	13 (29%)				

* Passing grade.

series 72-MYC-20 the passing grade of each set was based on the lowest mark attained by a referee laboratory. Thus, 70% was passing in the single letter series and 50% in the double letter series. Starting with series 72-MYC-48, 70% was established as the lowest passing grade and the average results of both series are shown in Table X.

It can be seen that the improvement in performance in mycology from 1972 to 1974 has been striking. The number of laboratories achieving a satisfactory grade was at a low point of 28 or 62% in 1972 but rose to 52 or 91% in 1974. Conversely, the number of laboratories performing poorly declined from a high point of 17 or 38% in 1972 to only 5 or 9% in 1974. Table X also reveals a noticeable decline in the number of laboratories participating in the program, especially in series 73-MYC-18 where specimens were distributed to laboratories only if they were equipped with a satisfactory, functioning Biological Safety Cabinet. This number has steadily increased as more laboratories acquired these cabinets.

Discussion

The improvement in performance in mycology may be attributed to two main factors. Probably the most important is the distribution of a critique of each series to laboratories with a permit in mycology (see General Discussion).

Another factor which may account for improvement is the decision of laboratories with a small volume in mycology, and poor-to-borderline performance, to relinquish their permits in this area especially when faced with the increased expense of the required Biological Safety Cabinet.

MYCOBACTERIOLOGY

This program was begun in April 1974 when 4 simulated sputum specimens in screw-capped sputum jars were delivered by examiners to laboratories with a permit for acid-fast smears and cultures, provided they were also equipped with a functioning Biological Safety Cabinet as required for this work.

Materials and Methods

Specimen Preparation and Distribution: Simulated sputa are prepared from a sterilized solution of 3% mucin (seeded with mycobacteria or other microorganisms, or left sterile), tubed in one-ounce, screw-capped sputum jars. These jars are placed in leak proof plastic bags, and then packaged in liquid-proof quart cartons which bear a biological hazard symbol.

All laboratories receive a shipment of 4 specimens twice a year. If a laboratory fails to achieve minimal standards on either set of specimens it will receive a third make-up shipment at a later date.

Laboratories with a permit for acid-fast smears are asked to prepare smears from the simulated sputa and report the following information within two days of receipt of specimen: the method for smear preparation (concentrated or direct), the type of stain used, the presence or absence of acid-fast bacilli in each specimen, and the quantity of organisms in positive smears, i.e., rare (3-9/smear), few (10 or more/smear), or numerous (1 or more in most fields).

Laboratories with a permit for acid-fast cultures are required to culture their specimens and to distinguish the pathogenic species, M. tuberculosis and M. bovis from other mycobacteria. These laboratories are asked to report the following information within 12 weeks: digestion-decontamination procedure, isolation media, observations on rate, kind and amount of growth, biochemical and other tests employed in identification, and final identification (group or species).

Laboratories that prepare smears and routinely inoculate cultures but do not identify cultures positive for acid-fast bacilli are tested only for their ability to report satisfactorily on the presence or absence of growth of acid-fast bacilli from the simulated specimens.

Determination of Validity of Specimens:

1. *Cultures.* Stock cultures are maintained on Lowenstein-Jensen slants in the refrigerator at 4°C, in the freezer at −20°C, and in skim milk at −20°C. Each culture is checked for characteristic morphology, typical reactions to key tests, and ability to survive in mucin solution for three weeks in the refrigerator (simulated field conditions). These are checked again for typical reactions and morphology before they are seeded in mucin for distribution to participating laboratories.

2. *Reference Laboratories.* For the first series, reference laboratories were selected either on the basis of consistently good performance in the New York City proficiency testing program in bacteriology or in the New York State proficiency testing program in mycobacteriology. In future series, reference laboratories will be chosen on the basis of consistently excellent performance in our program for acid-fast smears and cultures. A specimen in our first series was considered valid if at least a majority of the reference laboratories reported a specimen correctly and if 2 sets of specimens prepared from the same lot as those distributed to participating laboratories behaved typically when tested in our laboratory. To further determine the validity of the specimen, a reference laboratory which reports a result at variance with our own or others' may be asked to repeat the tests.

System of Grading:

1. *Acid-fast smears.* Each correct answer is accorded 25 points. 75% is considered a minimum passing grade. Full credit is given for the observation of

acid-fast bacilli in positive specimens regardless of quantity. No credit is given if acid-fast bacilli are reported in negative specimens.

2. *Acid-fast cultures.* A grade of 76%* is considered the minimum passing grade. The grading scheme is shown below:

Specimen negative for acid-fast bacilli and reported as such	—25 points
Negative specimen reported as positive for acid-fast bacilli	— 0
*Isolation of mycobacteria	— 5 points
*Differentiation of M. bovis and M. tuberculosis from other mycobacteria	—14 points
Correct Runyon Group	— 2 points
Correct species	— 4 points
Reported negative	— 0
Total accumulated points	—25

Results

A. *Summary of Results for Acid-Fast Smears in the First Proficiency Test Series 74-MYB-16*

- I. Number of:
    - Laboratories receiving specimens for acid smears—72
    - Smear reports returned—71
    - Smear reports not received—1
- II. Number of laboratories:
    - Receiving a passing grade of 75% or higher—64
    - Receiving a failing grade (lower than 75%)—2
    - Sending inconclusive results, not evaluated—1
    - Sending late (one month or later) reports and not evaluated—4
- III. (1) Number of laboratories using ”direct” smear preparation only—3
    - Number passing—1
    - Number failing—1
    - Number submitting inconclusive results—1
- (2) Number of laboratories using “concentrated” smear preparation only—33
    - Number passing—32
    - Number failing—1
- (3) Number of laboratories using “direct” and “concentrated” smear preparation—31
    - Number passing—31
    - Number failing—0
- IV. (1) Number of specimens which yielded a higher number of acid-fast bacilli when concentrated—70
- (2) Number of specimens which yielded a higher number of acid-fast bacilli in direct preparations—1

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* Minimum for passing = 19 points for each of 4 organisms

   (3) Number of specimens yielding equal numbers of acid-fast bacilli from both concentrated and direct preparations—59

B. *Summary of Results for Acid-Fast Cultures in the First Proficiency Test Series*

   I. (1) Number of laboratories that received specimens for acid-fast cultures—68

   (2) Number of culture-reports returned on time—56

   Laboratories that received a passing grade of 76% or higher—43 (77%)

   Laboratories that received a failing grade (lower than 76%)—13 (23%)

Discussion

A critique of the results of this first proficiency testing series was prepared for distribution to all participating laboratories. As additional data become available on proficiency in mycobacteriology, the impact of the program can be better assessed.

General Discussion

In summary, the initiation and maintenance of proficiency testing in these several areas of clinical microbiology have been responsible for an improvement in the performance of diagnostic laboratories in New York City. This change appears to be correlated with the stimulus of proficiency testing itself, as administered by a regulatory agency, but also with improved communications and educational programs, of both formal and informal types. Although difficult to document, the effects of a continuing productive interchange between our laboratories and those of participants reflect a response to the necessities of quality control, both external and internal. Daily contacts by participating laboratories through telephone consultations, personal visits, or individually requested training sessions provide an opportunity for all concerned to acquire current information on methodology, quality control, and a variety of problems encountered in their work.

To date, the most valuable of our educational programs, as measured by the results of proficiency testing, was the series of workshops given in diagnostic bacteriology. It is hoped that these can be continued from time to time in the future, and extended to other disciplines that have not as yet been offered. In the interim, however, we have found that the less expensive effort of providing a critique of each performance test (as initiated in mycology and adapted by other programs) also has great educational value. This summary usually includes a comparative report of the performance of all participating laboratories; a summary of the total number of laboratories receiving a passing and an unsatisfactory grade; comments on each specimen; suggestions for improvement of performance, including the addition of more pertinent tests; a review of current laboratory or clinical information on the organisms included in a test series; possible explanations for incorrect results; charts for differentiating microorganisms of similar properties; and an updated bibliography. With this information, many laboratories have become more aware of the scope and types of tests, and newer techniques required for adequate diagnostic microbiology, including the necessity for standardized methodology in antibiotic susceptibility testing. This type of critique has received a very favorable response from participating laboratories and will be continued as a part of our effort to encourage and assist in the maintenance of strong standards.

Addendum

The basic mechanisms of these programs have not changed since 1974 but some have been strengthened or expanded in a number of ways. For example, in bacteriology an optional ungraded specimen is now included in each proficiency test series. This specimen contains a single organism offered as an interesting or unusual species which may be new to many laboratories or easily misidentified. The general interest in this optional specimen has encouraged us to regard it as a valuable educational tool. In addition, the method of evaluating the graded specimens in bacteriology has been changed. A detailed evaluation sheet is now prepared for each participating laboratory on each testing occasion. This form provides a numerical grade, indicates the minimum satisfactory score, and the laboratory's rating (i.e., upper or lower half of those passing, or unsatisfactory).

In antibiotic susceptibility testing, the selection of the optional antibiotics to be evaluated is now made according to the standards proposed by the National Committee for Clinical Laboratory Standards (8). In addition, this laboratory currently offers a voluntary program of proficiency testing in staphylococcal phage typing.

Continued proficiency testing in mycobacteriology has resulted in a general improvement of performance, as well as the withdrawal of some laboratories displaying a poor or marginal capability in this area.

A new program of proficiency testing in parasitology was initiated in January 1975. This program includes evaluation of performance in the examination of blood smears for malaria parasites and of formalinized fecal specimens for intestinal protozoa and helminths. Our experience with this specialty, after five test series, parallels in general that reported here for other areas of microbiology. The program has served as a stimulus for improvement of standards where necessary, with a number of laboratories withdrawing or seeking additional training for their personnel. Some plans for workshops in parasitology are currently under way.

Acknowledgments

The programs in several aspects of microbiology described in this paper have been a part of a larger effort of the Public Health Laboratories, The City of New York, Department of Health, to set standards in all areas of clinical laboratory performance, including clinical chemistry,

hematology, and immuno-hematology. Under the general direction of Dr. Bernard Davidow, Assistant Commissioner for Laboratories, and Dr. Paul S. May, Deputy Director, these activities are conducted within the Division of Laboratory Improvement, headed by Miss Sylvia Blatt, Assistant Director. Without their collaboration and advice this work could not have been accomplished.

We also wish to pay tribute to the memory of Dr. Daniel Widelock, former Deputy Director, who participated in the initiation of these programs and whose effective role in their leadership was invaluable. His insight and objectivity were a constant stimulus in establishing and maintaining our goals.

Finally, we acknowledge with particular gratitude the effective contributions of the many professional colleagues, especially those in the reference laboratories, throughout this City and elsewhere, who gave freely of their time and efforts to help us mount and continue these programs; and the dedicated services of the field examiners who helped to build the bridge between our laboratories and those of participants.

References

1. Schaeffer, M. Health Department's Role in Improving Operations of Clinical Laboratories. Pub. Health Rep. 81: 71, 1966.
2. Schaeffer, M., Widelock, D., Blatt, S., and Wilson, M. E.: The Clinical Laboratory Improvement Program in New York City: I. Methods of Evaluation and Results of Performance Tests. Health Lab. Sci. 4: 72, 1967.
3. Schaeffer, M., Widelock, D., May, P. S., Blatt, S., and Wilson, M. E.: The Clinical Laboratory Improvement Program in New York City: II. Progress After Five Years of Experience. Health Lab. Sci. 7: 242, 1970.
4. Schaeffer, M. and Wilson, M. E.: Comparison of Different Approaches to Proficiency Testing in Microbiology.* Presented at the National Conference on Proficiency Testing, Center for Disease Control, Atlanta, Georgia, October, 1971.
5. Ericsson, H. M., and Sherris, J. Antibiotic Sensitivity Testing. Report of an International Collaborative Study. Acta. Pathol. Scandinavica. Sect. B. Supplement No. 217, 1971.
6. Bauer, A. W., Kirby, W. M. M., Sherris, J. C., and Turk, M. Antibiotic Susceptibility Testing by a Standardized Single Disc Method. Am. J. Clin. Path. 45: 493, 1966.
7. Kaufmann, W., Kelly, J. H., Vanderlinde, R., Fasce, C. F., Gordon, M. A., Stevens, R. W., and Gruft, H.: Clinical Laboratory Performance. Experience with New York State Clinical Laboratory Program. N.Y. State J. Med. 69: 1989, 1969.
8. National Committee for Clinical Standards: Performance Standards for Antimicrobial Disc Susceptibility Tests, July 1975.

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JOEL HARTLEY, M.D.
1910–1976

In Memoriam

JOEL HARTLEY, M.D.

1910–1976

The premature death of Dr. Joel Hartley is deeply mourned, not only by his colleagues on the orthopaedic service, but throughout The Mount Sinai Hospital and Medical School and by his many friends; for Dr. Hartley was one of the few and rare individuals who contributed and gave all his energies, both in the interest of this institution and of his patients, as he did in his own medical specialty.

Joel was a thorough New Yorker, was born, raised his family, and lived his life in the city. Yet with his well-balanced personality, he engaged in travel, active sports, and solitude in the country with his family. Dr. Hartley graduated from the College of the City of New York with a B.S. degree, and received his medical education at New York University College of Medicine where he graduated in 1935. After two years of rotating internship at Queens General Hospital, he came to Mount Sinai as an assistant in Morbid Anatomy under Dr. Paul Klemperer, where he developed an interest in musculoskeletal system, and a commitment to orthopaedics. At that time, perhaps the most outstanding academic orthopaedic program in the country was under the direction of Dr. Arthur Steindler, at the State University of Iowa. Dr. Hartley attended Dr. Steindler's program for one year, leading to his M.S. degree. He returned to Mount Sinai Hospital in 1940 as one of the first residents in the newly formed orthopaedic service. In March 1943, his residency was interrupted by a call to duty as first lieutenant during World War II. His three years of active duty were spent in the continental United States, mainly at general hospitals, being promoted to the rank of major and serving as chief of various orthopaedic sections.

Dr. Hartley returned to New York City to practice orthopaedics, and to Mount Sinai as an assistant attending in 1946. During the early part of his practice, he was orthopaedic consultant to the New York Cancer Institute, senior orthopaedist at the Veteran's Administration Hospital, orthopaedist at the Home for the Aged and Infirm Hebrews, and attending orthopaedist-in-charge at Lebanon Hospital; and was one of the founders and major supporters of the Health Insurance Plan of Greater New York for a large part of his medical career. As a Diplomate of the American Board of Orthopaedic Surgeons, Fellow of the American College of Surgeons, Fellow of the American Academy of Orthopaedic Surgeons and of the New York Academy of Medicine, he participated actively in their meetings and programs. At Mount Sinai, where Dr. Hartley rose to the rank of attending, and clinical professor of orthopaedics, he was intimately involved in programs and policies of the hospital and school, having served on, and chaired, many committees, and having been president of the Association of the Attending Staff and the Alumni Association, as well as lecturer at the Nursing School and faculty member of the Page and William Black Post-Graduate School of Medicine. Characteristic of his deep and personal concern for his own patients and the welfare of patients at the hospital, most of his committee involvements were in the area of patient care, having developed one of the most comprehensive analyses and set of recommendations regarding patient needs for the Medical Board. His skill in administration, and understanding of fundamental problems was of great help in the growth of the orthopaedic program in the hospital and medical school, most notably his leadership in medical audits. Dr. Hartley, with Dr. Bernard Simon, served as co-chief of the hand team in developing a combined program between orthopaedics and plastic surgery that has grown enormously. He was a member of the Orthopaedic Research Society where he presented his experimental observations on the osteogenetic effect in muscles of an injected abstract derived from bone, and a method of maintaining viability of a bone graft by transplanting it along with vascular supply maintained through a muscle pedicle. His publications on Reflex Hyperemic Deossification, and Osseous Changes and Fractures in Malabsorption Syndrome were evidence of his broad interests and knowledge of physiology and medicine in management of musculoskeletal problems.

Characteristic of Dr. Hartley's courage and humanitarianism was an episode in 1968 on a trip to Africa. He and his wife chartered a small plane to fly to the Ngorongoro crater in Tanzania. Caught in a fog, the plane crashed into the mountainside. In spite of his own fractured ribs and spine, Dr. Hartley was able to stop the bleeding of a severe hemorrhage suffered by the pilot, treat lacerations and wounds of other passengers, and administer sedatives. After six hours he reached the road and obtained help. Dr. Hartley credited his practice of always carrying a well-equipped first-aid kit wherever he went as having "saved the day." Subsequently, his interest in first aid and emergency treatment became intensified and resulted in a successful book for the layman and physician, *First Aid without Panic*, and a popular, well-attended course in first aid and emergency care at the Page and William Black Post-Graduate School.

Perhaps one of the most beautiful, special, and joyous aspects of his life, was the intimate and happy relationship that Joel and Freddie Hartley had for 42 years of marriage. As their children, Leslie and Sally grew up in New York, the Hartleys, in their close, active and understanding way of life, touched warmly upon the lives of many other postwar families of colleagues and friends in all walks of life. As a member of the hospital family, Dr. Hartley was affectionate, perceptive, sensitive and loyal, being unselfish in making available his time and efforts in bedside teaching and patient care at rounds and conferences with house staff and students. We are fortunate, and much better off in our lives, having enjoyed Joel's humor, gentleness, friendship, kindness, spirit, and companionship which we will miss, but never forget.

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Studies on Inflammatory Bowel Disease*

F. WARREN NUGENT, M.D.

Discussing inflammatory bowel disease at the home of Crohn's disease is a classic example of carrying coals to Newcastle. To present to this audience a lecture that is in any way a review of the literature on the subject would be most inappropriate, since much of this literature has originated within these walls. I would, therefore, like to discuss some of my recent personal interests in inflammatory bowel disease.

Ulcerative Proctosigmoidostomy

Ulcerative proctosigmoiditis (1) is a type of "distal" colitis that is characterized by typical sigmoidoscopic findings of ulcerative colitis in the rectum and, at times, in the sigmoid, with normal barium enema findings proximal to this area. We include only patients in whom the disease has been confined to this area for at least a two-month period so as to exclude those in whom distal disease is simply the beginning of a more extensive process. We reviewed charts of 234 patients with a mean follow-up of 8.2 years and a total follow-up of approximately 2,000 patient years. The average age at onset was later than that observed in patients with diffuse colitis. Rectal bleeding, present in all patients, was the foremost symptom. Less than half of the patients ever experience diarrhea, which is usually mild when present. Most patients have normal bowel movements and some are constipated. Systemic symptoms are uncommon; significant weight loss was present in only 15% and anemia in 2%. Anorectal complications, invariably short-lived, occurred in 7%. Extracolonic complications were virtually absent with only one patient complaining of significant arthralgias. None of the other distressing extracolonic manifestations were noted. Malignant degeneration was not observed despite the long follow-up period.

Most patients responded well to a conservative medical approach that did not include the use of systemic steroids. Twelve percent of the patients had proximal extension of disease at some time, but only 4% required operation. This is in contrast to our experience of approximately 65% operative intervention in patients with diffuse ulcerative colitis.

The major lesson learned from this study is that distal colitis is usually a benign process which responds to conservative treatment. Both the patient and the physician must keep in mind that this form of colitis is not likely to extend and rarely requires operative intervention.

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* Paper presented at The Mount Sinai Hospital, New York, N. Y., February 25, 1976.

From the Department of Gastroenterology, Lahey Clinic Foundation, Boston, Ma. 02215.

Requests for reprints should be sent to: F. Warren Nugent, M.D., Lahey Clinic Foundation, 605 Commonwealth Avenue, Boston, Ma. 02215.

Prognosis after Resection for Colonic Crohn's Disease

A problem of interest to your group and mine is that of recurrent Crohn's disease after operation. We reviewed retrospectively 194 consecutive patients who had undergone colectomy for inflammatory disease of the colon in the late 1950's (2, 3). They were classified by clinical and pathologic criteria into three groups: ulcerative colitis, Crohn's colitis, and colitis of indeterminate type. The four clinical criteria for the diagnosis of Crohn's colitis were the presence of chronic, recurring perianal disease or the presence of colonic fistula, or the absence of rectal bleeding at all times or the absence of proctoscopic abnormality during activity of the disease. Patients who did not manifest these criteria were classified clinically as having ulcerative colitis. There was no clinical classification of colitis of indeterminate type.

Microscopic sections were available on all patients and were reviewed independently from the clinical review. The pathologic diagnosis was Crohn's disease when one or more of the following three criteria were present: granulomas, fissures extending into the muscularis, or transmural inflammation and fibrosis remote from mucosal ulceration. Only those granulomas not associated with mucosal ulcers were accepted.

Radiologic criteria were not used for classification because too few radiographs were available for review.

In order to differentiate reactive ileal inflammation from ileal Crohn's disease the same criteria were used as those applied to the colon. Mucosal inflammation or superficial ulceration was not considered evidence of ileal involvement unless accompanied by one or more of the previously mentioned criteria.

The diagnosis of ulcerative colitis was made in all patients with inflammation and ulceration confined to the mucosa and submucosa and without granulomas. In some patients, the pathologic changes were not consistent with either Crohn's disease or ulcerative colitis and were called colitis of indeterminate type.

Of the 194 cases, 60 had clinical evidence of Crohn's disease: chronic perianal disease, 40; normal proctoscopic examination, 25; absence of rectal bleeding, 19; and colonic fistulas (other than perineal), 6. Fifty-nine patients had pathologic evidence of Crohn's disease: granulomas, 45; transmural inflammation and fibrosis, 41; and fissures, 21. Using these groups of clinical and pathologic criteria and accepting the presence of either as diagnostic, the diagnosis of ulcerative colitis was made in 99 patients (51%), Crohn's colitis in 76 patients (39.2%), and indeterminate colitis in 19 patients (9.8%). The clinical and pathologic diagnoses corresponded in approximately 75% of cases.

Of the 76 patients with Crohn's disease, 58 had a total proctocolectomy with ileostomy as the primary or subsequent operative procedure. Five patients died in the postoperative period, leaving 53 at risk for recurrence. Recurrent Crohn's disease developed in the ileum in three patients (5.7%). These 58 patients were classified as having Crohn's disease by either clinical or histologic criteria. If the diagnosis of Crohn's disease is limited to only those patients whose disease fulfills histologic criteria, 46 patients, there were 43 patients at risk for recurrence. Recurrent disease developed in three patients (7.0%).

Anastomotic procedures were carried out in 28 patients. Ten of these subsequently required proctocolectomy because of recurrent disease. Of the other 18, 4 required further resection and reanastomosis, 4 had recurrent disease treated medically, 1 died after operation, and 9 patients have been followed for 11 to 17 years (average mean, 13 years) without evidence of recurring Crohn's disease.

We found no significant difference in the number of ileal revisions in the group with Crohn's colitis compared to the group with ulcerative colitis. Of patients with ulcerative colitis, 23% required revision and 29% of those with Crohn's colitis also required revision. None of the patients in either group had histologic criteria for the diagnosis of Crohn's disease.

In our experience, therefore, the outlook after proctocolectomy and ileostomy for inflammatory disease of the colon is not greatly different whether the patient has Crohn's disease or ulcerative colitis. A possible source of error in our findings is the relatively small group of patients with Crohn's disease, but it seems unlikely that this would make a great difference. In contrast, when an anastomotic procedure was carried out in patients with Crohn's disease of the colon, recurrence, usually requiring further resection, developed in two-thirds of all patients.

We are not suggesting that proctocolectomy and ileostomy should be the primary operative treatment of choice in Crohn's disease of the colon. If the patient has a normal rectum and the perineum is not significantly involved, an anastomotic procedure may be performed. If proctocolectomy and ileostomy is required, there should not be undue concern about the possibility of recurrence in the ileum.

Serum Lysozyme in Inflammatory Bowel Disease

As a change of pace, I would like to discuss a new diagnostic method. The diagnosis of Crohn's disease is not easily established even when it is suspected, and the differential diagnosis between Crohn's disease and ulcerative colitis may be difficult even when all clinical, radiographic, and histologic data are available. It has recently been reported that the level of serum lysozyme will establish this differential diagnosis. We undertook a study to attempt to confirm these findings (4).

Lysozyme assays were performed by a turbidimetric procedure utilizing Micrococcus lysodeikticus as the substrate, and hen's egg white lysozyme as the standard. The procedure employed was that of Litwack as modified by Worthington Bio-Chemical Corporation. Results of this photometric procedure were compared to those obtained with the lysoplate radial diffusion method, and no significant difference between the two methods was detected. Blood samples for the assay were centrifuged immediately, and the serum was frozen at −20°C. The assays were performed in duplicate within three weeks of collection.

Patients were divided into three groups: controls, those with ulcerative colitis, and those with Crohn's disease. The diagnosis was based on generally accepted criteria. Activity of the disease was arbitrarily classified as remission, mild disease, moderate activity, or severe activity. None of the patients had evidence of other types of granulomatous disease.

There were 49 patients in the control group, 19 men and 30 women, with an age range of 18 to 77 years. There were 21 patients in the ulcerative colitis group, 12 men and 9 women, with an age range of 18 to 75 years. Activity of disease was classified as severe in 2, moderate in 2, mild in 11, and remission in 6.

There were 63 patients in the Crohn's disease group, 30 men and 33 women, with an age range of 20 to 73 years. Twenty-one patients had large bowel involvement, 29 had both colonic and small bowel disease, and 13 had disease confined to the small bowel. Activity of the disease was severe in 6, moderate in 13, mild in 23, and remission in 21.

The mean serum lysozyme concentration in micrograms per milliliter for each group was control, 7±2; ulcerative colitis, 7±2; and Crohn's disease, 10±4. A significant difference in serum lysozyme concentration was observed between the group with Crohn's disease and the other two groups ($P < 0.0005$). Based on these data, the upper limit of normal was established as 11 mg per milliliter (mean, ±2SD). Only one patient in the control group had a serum lysozyme level greater than normal, and none of the patients in the ulcerative colitis group fell in the abnormal range.

Of the group with Crohn's disease, 43 patients (68%) had serum lysozyme levels of 11 mg per milliliter or less, and 20 patients (32%) had levels greater than 11 mg per milliliter. No relationship was detected between serum lysozyme levels and the location or the severity of the disease.

The results of this study do not confirm previously reported findings, and the differences cannot be explained by patient selection, site of disease, or severity of disease. Similar patient groups were used in both studies. It is possible that the different methods for assay of lysozyme could explain the conflicting results, but the reason for this is not clear, as we found no significant difference in results between the two methods.

Our results do not preclude the use of serum lysozyme determination in the differential diagnosis of Crohn's disease. Although only 32% of patients with Crohn's disease had an elevated serum lysozyme level, this elevation, when present, is strongly suggestive of Crohn's disease. Obviously a larger group of patients should be studied and further comparisons made between the different methods of assay.

Crohn's Disease of the Duodenum

I conclude with a discussion of one of our recent interests, Crohn's disease of the duodenum. This is not a common disease, having been reported in approximately 165 cases. Almost all of these cases are described in small scattered reports, however, and a good clinical review of the topic is lacking. We have encountered 36 patients with Crohn's disease involving the duodenum (5). This group represents approximately 2% of the total population of new patients with Crohn's disease seen during a 20-year period.

The diagnosis of duodenal Crohn's disease was established by one of two criteria: the histologic finding of noncaseating granulomatous inflammation of the duodenum with or without obvious Crohn's disease elsewhere in the intestinal tract and without evidence of a systemic granulomatous process and Crohn's disease of the small or large bowel and diffuse inflammatory change in the duodenum considered to be a typical radiologic sign of Crohn's disease.

There were 25 men and 11 women in the group. Age at onset varied from 5 to 59 years (mean, 27 years). Nineteen patients appeared to have the onset of duodenal disease coincident with the onset of disease elsewhere in the gastrointestinal tract, 11 patients had obvious disease elsewhere from 4 to 40 years before development of duodenal disease, and 6 patients had disease which at onset was confined to the duodenum with or without involvement of the gastric antrum. In one of the latter six patients, terminal ileitis developed 4 years later, in one patient widespread jejunal disease in continuity with the duodenum developed 7 years later, and in a third patient severe diffuse gastric Crohn's disease requiring total gastrectomy developed 20 years later. In the other three patients (all histologically verified) the disease remained confined to the duodenum throughout its course, although all three had involvement of the gastric antrum.

Of the 32 patients who had Crohn's disease elsewhere in the gastrointestinal tract (excluding the stomach), 1 had esophageal disease, 5 had disease in the proximal small intestine, 16 had disease in the terminal ileum, 7 had disease in the colon, and 3 had widespread disease throughout the small and large intestine.

Epigastric pain was by far the commonest symptom. Most commonly, pain was postprandial and accompanied by nausea and at times vomiting. Some patients had pain that was suggestive of duodenal ulcer pain, since it was relieved by food or antacid therapy. In the majority of patients, symptoms reflected degrees of gastroduodenal obstruction. Significant weight loss was common, and major upper gastrointestinal bleeding, presenting as hematemesis or melena, occurred in five patients.

Radiologically, three patterns of disease were noted in the duodenum. The first and commonest was contiguous involvement of the gastric antrum and proximal duodenum. Of the 36 patients, 20 had this radiologic pattern of involvement (7 others had histologic evidence of gastroduodenal disease with radiologic changes confined to the duodenum). The second pattern, found in six of the patients, was involvement of an isolated segment of descending duodenum. The third pattern was involvement of the distal duodenum (three patients in this group). All of these patients had contiguous involvement of at least a short segment of proximal jejunum. On radiologic examination, irregular thickening, edema, and a cobblestone pattern of the mucosa were seen. As the disease progressed, stenosis, eventually becoming severe, was commonly seen. Fissures and pseudodiverticula were occasionally noted. Barium refluxed into the common bile duct and pancreatic duct in one patient. In some patients with gastroduodenal involvement, progressive stenosis of the pyloric area produced a pseudo-Billroth I appearance with loss of identity of the pylorus.

Endoscopic examination was carried out in 17 patients and biopsies were obtained. The mucosa of the involved antrum and duodenum was diffusely granular with some nodularity and varying degrees of ulceration. Usually the ulcers were superficial, but at times they were deeper and linear. The involved area was stiff, lacked distensibility, and contained varying degrees of stenosis.

On histologic examination, when full-thickness biopsies were available, chronic inflammation and fibrosis were found to involve the entire duodenal wall and noncaseating granulomas were observed. The granulomas could be detected in any layer of the duodenal wall or in the regional nodes. The histologic changes were identical to those seen in Crohn's disease occurring elsewhere.

Twenty-eight of our patients had histologic specimens available for review that were obtained either by operation or by endoscopic or capsule biopsy. Of the 28 patients, 12 had all features of Crohn's disease, including granulomas. In 16 patients, no granulomas were identified, but other changes consistent with the diagnosis of Crohn's disease were present. Of the 17 endoscopic biopsies, none demonstrated granulomas. A gastric specimen obtained from one of three patients by a capsule biopsy revealed granulomas.

Twenty of the 36 patients were operated on for obstruction of the pylorus or duodenum. Of these, 18 patients had a bypass procedure; of these 18 patients, 15 continue to be free of all significant upper gastrointestinal symptoms 1 to 19 years later (average, 6.6 years). One patient died six years after operation from extensive Crohn's disease of the entire gastronintestinal tract, all of which was present before duodenal surgery. Two patients have had local extension of disease beyond areas that were involved at the time of operation. One of these patients after a Billroth II resection, had severe Crohn's disease of all remaining stomach. Four years after the original procedure, total gastrectomy with esophagojejunostomy was required. Histologic examination of the resected stomach revealed noncaseating granulomatous disease. This patient has never had Crohn's disease elsewhere in the gastrointestinal tract. In the second patient, widespread local extension developed four years after gastroenterostomy. Both the distal stomach and proximal jejunum were involved. Two patients underwent operations that did not bypass the duodenum. One patient had pyloroplasty and is symptom free 11 years later and the other patient had duodenectomy and died in the postoperative period.

Sixteen patients were treated medically; 12 of the 16 patients have received steroids intermittently. Of these 12, 4 now have no significant symptoms at 1, 2, 6, and 6 years follow-up; 5 have moderate symptoms and moderate disability, 2, 4, 6, 14, and 14 years later; and 3 have died, all with widespread Crohn's disease which had been present from the onset of their disease. Four patients were treated conservatively without steroid therapy; of these patients, two have no significant symptoms 9 and 15 years later and two have mild to moderate symptoms and disability 1 and 2 years later.

Duodenal Crohn's disease appears to involve 0.5 to 4% of the total population of patients with Crohn's disease. Age and sex distribution are not unlike that of Crohn's disease located elsewhere. The patient usually, but not necessarily, has obvious Crohn's disease elsewhere in the gastrointestinal tract. Clinically, the patient with duodenal Crohn's disease presents with upper abdominal pain usually localized to the epigastrium, and in some patients it is difficult to differentiate Crohn's disease from peptic ulcer. This differential diagnosis must depend upon radiologic, endoscopic, and, if available, histologic findings. Pancreatitis did not develop in any of our patients, although one patient had reflux of barium into the pancreatic and bile ducts. Legge et al (6) reported evidence of pancreatitis in 4 of 11 patients with duodenal Crohn's disease, all 4 of whom had reflux into the pancreaticobiliary tree.

On radiographic examination, most patients had changes involving the proximal duodenum. Obviously the pylorus is not a barrier to the extension of Crohn's disease, as all of our patients with involvement of the proximal duodenum also had involvement of the distal stomach, although gastric involvement was not always apparent radiographically. A few patients had involvement of an isolated segment of mid-duodenum and a few, involvement of the distal duodenum in continuity with the proximal jejunum.

The endoscopic findings were, for the most part, nonspecific. Unfortunately, endoscopic biopsy specimens rarely yield granulomas, probably because the specimens are too small and granulomas tend to be located in deeper layers of the duodenal wall.

Medical treatment, using methods similar to those for Crohn's disease found elsewhere in the gastrointestinal tract, is the therapy of choice in all nonobstructing disease. If obstruction develops, bypass surgery is indicated, and, as our experience and that of others suggest, it is accompanied by an excellent chance of long-term relief of the duodenal symptoms.

References

1. Nugent, F. W., Veidenheimer, M. C., Zuberi, S., et al: Clinical Course of Ulcerative Proctosigmoiditis, Am J Dig Dis 15:321–326 (April) 1970.
2. Nugent, F. W., Veidenheimer, M. C., Meissner, W. A., et al: Prognosis after Colonic Resection for Crohn's Disease of the Colon, Gastroenterology 65:398–402 (Sept) 1973.
3. Nugent, F. W., Veidenheimer, M. C., Meissner, W. A., et al: (Letter to the Editor) More on the Course of Crohn's Disease of the Colon, Gastroenterology 66:629 (April) 1974.
4. Nugent, F. W., Mallari, R., George, H., et al: Serum Lysozyme in Inflammatory Bowel Disease, Gastroenterology 70:1014–1016.
5. Nugent, F. W., Richmond, M., and Park, S.K.: Crohn's Disease of the Duodenum, Gut (In press).
6. Legge, D. A., Hoffman, H. N., Carlson, H. C.: Pancreatitis as a Complication of Regional Enteritis of the Duodenum, Gastroenterology 61:834–837 (Dec) 1971.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

The Program-Resource Concept for Hospitals: An Alternative Management Strategy

SAMUEL DAVIS, M.S.* AND WILLIAM D. CARSWELL, M.S.I.E.†

The rapidly increasing size and complexity of the modern hospital and medical center have made the classic managerial functions of planning, operating, and controlling more difficult to perform, yet these functions are essential to the stability and growth of the organization. Most traditional, functional organizational structures have evolved to a point whereby effective management of the organization's resources is hindered, if not made impossible, because of reliance on personal experience and knowledge, of the structure and dynamics of the organization for success in decision-making.

What is needed in today's hospitals is an underlying science, or at the very least a more structured, less personalized approach to organization and management. This kind of philosophy has been loosely termed the "systems approach."

The systems approach is primarily a way of thinking about the job of managing. It affords a framework for integrating into a whole the internal and external environmental factors and the diverse operations that affect the success of an organization. It recognizes subsystems within which the manager must operate. The systems concept advances a way of thinking that helps to explain some of the complexity of the manager's environment and also assists the manager in the decision-making process.

Although the adoption of systems theory in hospital management is a fairly recent development, this trend is likely to accelerate. More and more hospitals are beginning to realize the importance of such an approach and the need to redesign their organizational and managerial systems for decision requirements. This evolution of management style has necessitated the development of a different type of manager, a generalist who understands mixed disciplines and the need to relate diverse operations and specialties toward a defined systems purpose—in hospitals, the efficient and effective delivery of health services to appropriate target populations. It is becoming increasingly important that today's hospital manager understand and practice the fundamental tenets of the systems approach.

The authors' experiences in large institutions and now at The Mount Sinai Medical Center in New York have reinforced the conviction that hospital organization and management as we generally observe is not likely to continue in its present functional form. This disparity between traditional organizational/managerial style and the need to define and accomplish institutional purposes has required a comprehensive reorganization of Mount Sinai's operation.

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* Director of The Mount Sinai Hospital and Senior Vice-President of The Mount Sinai Medical Center, New York, New York; Associate Professor of Administrative Medicine, Mount Sinai School of Medicine of The City University of New York, New York.

† Senior Consultant, The Mount Sinai Hospital, New York, New York.

Requests for reprints should be sent to: Mr. Samuel Davis, Director, The Mount Sinai Hospital, Fifth Avenue and 100 Street, New York, N. Y. 10029.

This program restructuring at Mount Sinai is now underway and is enhanced by the introduction of various management science disciplines and methodologies. The intent of this paper is to present our viewpoint for integrating various organizational and managerial techniques to achieve an effective system for managing hospital operation. We do not contend that the particular systems approach to management as defined at Mount Sinai is the only road to effective management, but we do believe that the particular organizational structure proposed, supported by suitable management techniques, is a realistic system for effective hospital administration.

We feel such an approach is not only appropriate for a 1200-bed medical center hospital such as Mount Sinai, but is totally applicable and necessary for any size hospital or health care institution. Specifically, we will show how the program-resource organization structure, various planning and budgeting methods, and an appropriately designed management information system (MIS) are integrated to provide the decision-making capabilities required in the environment of the modern hospital.

Organizational Structure

The increasing complexity of modern hospitals, combined with adherence to the hierarchical, monolithic organization is viewed by several writers as an underlying deterrent to effective management (1, 2, 3). Without an organizational structure that reflects the goals and philosophies of a complex institution, there is little possibility that a manager can successfully direct the activities of that institution.

Today's hospital environment requires an organizational structure that simultaneously accounts both for the collegial, participatory decision-making structure for directing health professionals and the hierarchical, centralized decision-making structure for managing unskilled workers (2). This structure has been termed a 'matrix organization.' Such an organization is shown in Figure 1, that of The Mount Sinai Hospital.

On the horizontal axis of this matrix are those managers who control institution resources—its personnel, matériel, spaces, and finances. These managers include the directors of nursing, support services, personnel, and finance. On the vertical axis are the physician-managers who control the institution's programs—typically separated into Medicine, Surgery, Psychiatry, etc. The importance of the program dimension in management is particularly relevant in teaching institutions, where the actions of full-time medical staff directly influence the use of the hospital's resources.

At Mount Sinai we have implemented the program-resource concept, a form of matrix organization. Under this system of management, almost every hospital employee serves two designated "masters," one for program function and one for resource function. This allows the hospital employee to have dual

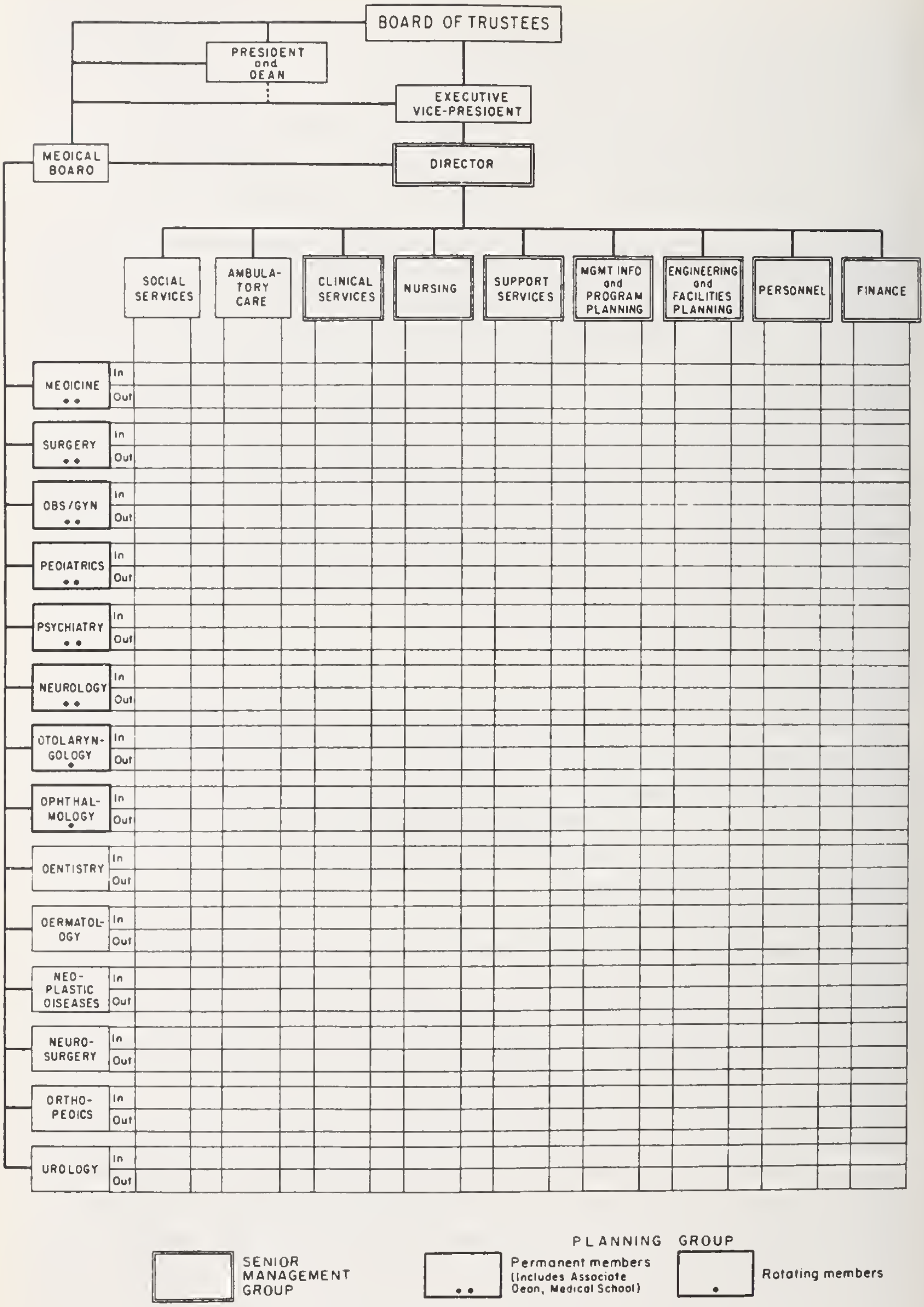
BOARD OF TRUSTEES
PRESIDENT and DEAN
EXECUTIVE VICE-PRESIDENT
MEDICAL BOARD
DIRECTOR
SOCIAL SERVICES
AMBULATORY CARE
CLINICAL SERVICES
NURSING
SUPPORT SERVICES
MGMT INFO and PROGRAM PLANNING
ENGINEERING and FACILITIES PLANNING
PERSONNEL
FINANCE
MEDICINE
SURGERY
OBS/GYN
PEDIATRICS
PSYCHIATRY
NEUROLOGY
OTOLARYNGOLOGY
OPHTHALMOLOGY
DENTISTRY
DERMATOLOGY
NEOPLASTIC DISEASES
NEUROSURGERY
ORTHOPEDICS
UROLOGY
In
Out
SENIOR MANAGEMENT GROUP
PLANNING GROUP
Permanent members (Includes Associate Dean, Medical School)
Rotating members

Fig. 1. The Mount Sinai Hospital Table of Organization, January 1976.

identification. Through the program resource concept, the senior clinical nurse is able to identify not only as a member of the program department, but simultaneously as a member of the nursing profession. Similarly, other health resource personnel are able to identify both with their profession and with their treatment team.

The basic functions of a resource-department head are to recruit and hire personnel, train them in the discipline of the department, assign them to program responsibilities, supervise their work within the discipline, evaluate and promote them within the discipline, and dismiss those whose performance is unsatisfactory. The resource-department head also serves as a consultant in his/her discipline to the program directors.

While resource-department heads have responsibility for setting objectives that relate to their own disciplines and for the resources for which they are responsible, program directors also are able to function effectively under a system of management by objectives. Each program director must develop a general statement of objectives for their program. The measure of their performance is how well they achieve stated objectives. If resources are committed to the program consistent with those objectives, they are obliged to carry out the objectives. If resources cannot be committed, they may reduce program objectives in scope and content. Thus, the program-resource concept establishes a clear basis for organizational accountability and the development of measures of performance.

Under the program-resource concept at The Mount Sinai Medical Center, the President/Dean and the Executive Vice-President establish broad hospital objectives. The overall program determination and the recommendations to the Board of Trustees for program priorities are their primary responsibilities. Under this system, the hospital director has two basic responsibilities: to answer to the governing board for the effective use of the hospital's resources, and to serve as a consultant to the President/Dean, Executive Vice-President, and program directors concerning application of the management process to achieve the hospital's and medical center's objectives. In this regard, the hospital director helps to define programs, to determine the necessary resources, and to develop targets and effectiveness measures on how well the program goals have been achieved.

In the program-resource concept at Mount Sinai, the principal organizational objectives are set forth as programs, and resources are identified as serving those programs. By such devices, problems of employee identification are addressed, cost control and program budgeting are made possible, task specialization is rationalized, and, most important, scarce health personnel have time to do the work for which they were trained. The measure of effectiveness of this organizational approach is whether, indeed, program outputs or purposes do improve against the agreed upon target of program performance. The program-resource concept is one solution to the problems of complex medical care organization.

We have described both the beginning and the end point of most program resource or matrix reorganizations in hospitals. What will typically remain unchanged are methods of planning, operating, and controlling that must *support* the program-resource organization philosophy. Specifically, we will discuss how, at Mount Sinai, program planning and budgeting, zero-base budgeting, financial modeling, and a management information system are integrated to sustain the organizational and managerial structure.

Planning and Budgeting

The public's awareness that it is paying greater amounts for health care has dictated that management techniques for accountability be developed. The program-resource concept makes possible accurate cost analysis and cost control through application of program planning and budgeting. That is, the resources required to meet program objectives—personnel, money, matériel, and facilities—should be planned and budgeted to reflect the cost of each program at its inception and annually thereafter. Departmental budgets also should be prepared to reflect the allocation of its resources on a functional basis and to meet the requirements of uniform accounting, particularly third-party reimbursement. Such budgets also provide a valuable management tool to the department head and to the hospital administration.

As applied at Mount Sinai, the program-resource concept will result in two complementary operational budgets, one showing the cost of the resources, the other the cost of each program. If the resources used in each program are allocated properly, their cumulative costs will equal the overall program cost. Organizational accountability and responsibility for manpower costs can thereby be appropriately assigned.

Program planning and budgeting in itself will not control the spiraling costs of operating a modern hospital. It is a tradition firmly based in virtually all health care institutions to sustain all operations at current activity levels for the next budgeting year and to consider in depth only those new operations that will compete for the institution's resources. Inherent in this budgeting scheme is a yearly quantum jump in the bottom line of the institution's operation. Even if a revenue or expenditure ceiling is known in advance (which is not commonplace), the trade-offs among programmatic activity cannot be objectively negotiated without serious harm to the administrator-program director relationship.

There is, however, an approach developed by Peter Pyhrr (4) called zero-base budgeting which addresses many of the problems encountered in traditional budgeting. Simply, the concept is to identify and define programmatic activities, categorize and describe programmatic activities in "decision packages," analyze and reduce or augment these packages, assign a priority to them, and finally apply the estimated revenue (or expense) ceiling to determine those that are to be included in the budget and those that cannot be included.

Because the zero-base approach delineates and analyzes each discrete activity in the hospital, it not only provides detailed budgetary input, but also specifies activity objectives, resources required, alternative modes of activity considered, and performance measures for subsequent operational audits. This approach is consistent with the management by objectives philosophy *and*, at Mount Sinai, provides a base for implementing routine management reporting on program and resource performance.

The advantages of the zero-base approach over traditional budget cycling are well-documented by Pyhrr and others. The most important attributes realized in our approach at Mount Sinai include its ability to: spotlight activity redundancies, specify program priorities, allow interprogrammatic comparisons, focus on whole programs rather than program marginal increases, and avoid budget recycling when revenue or expense ceilings change. However, program budgeting and zero-base methods are not easy to implement. Much consideration must be given to potential disaster as a result of insufficient indoctrination and inadequate process definition. But, a well-planned and designed budgeting system can provide the vehicle objectively to meet institutional goals and simultaneously to avoid constant disparities in bottom-line revenues and expenses.

How can bottom-line revenue be determined for the forthcoming budget year? Mount Sinai is now integrating a financial planning simulation model with the program/zero-base budgeting approach described above. This modeling capability will allow for an iterative process of program structuring and revenue optimization. That is, the expected revenue for a mandated base of programs will be derived from the model simulation. As "optional" revenue- and nonrevenue-generating activities in order of priority (as derived through the zero-base process) are incrementally added to that base, a revenue sensitivity is noted. Trade-offs among the program decision packages can then be made to optimize the use of anticipated revenue generated by the mix of program activity and supporting resources. This approach not only avoids deficit spending but also provides a methodology for achieving institutional goals in the most cost-effective manner.

To this point we have discussed how the program-resource organization concept and the requisite planning and budgeting techniques are being developed and implemented at Mount Sinai Hospital. However, this or any organizational and managerial framework depends on a Management Information System (MIS) that is responsive to the various needs of managers in all phases of planning, operations, and control. The MIS is the basis for any effective management structure. As such, we have offered an overview of MIS attributes and some recommendations for its development.

Management Information System

"Information systems" and "management information systems" have only recently become accepted parts of our vocabulary. However, the understanding of their meaning has not corresponded to the word's increased usage.

An information system is the procedure or mechanism whereby numeric, alphabetic, graphic, photographic or other information is gathered, stored, perhaps rearranged, and retrieved. A *management* information system provides such information in various formats and detail levels for purposes of decision-making in the management functions of planning, operations, and control.

In addition to merely providing appropriate data to which the manager might refer as he or she makes decisions, a true MIS also directly supports and assists the decision-making process. Where the typical information retrieval system might only provide a historical record, the MIS can highlight exceptions, predict consequences of alternatives, or even prescribe optimal courses of action. For example, at Mount Sinai, the MIS provides, among other uses, various managerial levels with appropriate productivity reports in which actual performance is compared to predetermined standards, workload forecasts are derived for future periods, and employee work schedules are generated which match available personnel with anticipated workloads.

To make the hospital more manageable, particularly in the program-resource organization which expands informational needs, we must design, implement, and utilize better management information systems. Information and its use in the decision-making process is not only a prerequisite but is in general *the* prerequisite for good institutional management in the health care field.

The needs for management information systems can be expressed in terms of the three principal functions of management—planning, operations, and control. These are summarized below in an order that facilitates our presentation.

Controlling is the process of assuring that the functions being managed are adhering to an agreed-upon plan and are achieving predetermined objectives. Clearly, the key ingredient for successful control is the feedback of suitable information in a format which allows corrective action. Upon reflection, it is rather easily seen that the characteristics of a good control system are virtually equivalent to those of a good management information system. That is, managerial control will be enhanced as MIS is enhanced. The two are almost synonymous.

Planning includes such activities as assessment of current and future demands, evaluation of alternative courses of action, specification of those programs and systems which are to be undertaken, development of program objectives and criteria for success, and the budgeting process. These are not independent activities.

The attributes of the MIS are ideally suited to gather, analyze and structure the kind of data base required for program and resource planning. The properly developed MIS should provide a mechanism to relate resources to activities, i.e., to convert various alternative programs or program activity levels to resource requirements. Thus, the MIS not only supports both the control function and the planning function, but it also serves as the link to tie the two functions together. The control (feedback) system provides cost-effectiveness productivity information to feed the planning process; and planning develops the standards and expectations used by the monitoring component of the control process. The only conclusion that can be drawn is that without MIS there is not adequate management planning or control.

Operations includes those day-to-day activities necessary for organizing and directing hospital processes. Since the hospital is such a labor-intensive "business," operating 24 hours a day for seven days a week, and responding to demands which are in part unpredictable, the most important operational management activity is that of personnel staffing and scheduling.

The types of management information required to support personnel scheduling and other operational functions are not unlike those for planning and control. However, routine operating decisions require a more sophisticated MIS in terms of timeliness and detail. The added costs associated with such enhanced day-to-day decision-making capabilities are significant, but not of the magnitude of the costs intrinsic in inefficient trial and error personnel scheduling methods now in general use. Without this operational component of MIS the potential benefits of the planning and control MIS functions cannot be fully achieved. It is only through a fully integrated and sufficiently detailed MIS that the real advantages of such a system may be realized.

We have indicated above the general needs a hospital MIS must adequately address. In developing such a system at the Mount Sinai Medical Center, we have identified and will be implementing certain strategies of MIS design necessary to support a program-resource organization. The following are recommendations that we feel are among the most critical.

—The management information system is not a separate system to be added to the top of the traditional information systems. The MIS must be fully integrated with the general accounting system, patient accounting, personnel/payroll, statistical reporting, inventory control, census, and the like.

—Remove the data processing department from the exclusive sphere of finance. Our recommendation merely reflects the concept that data processing should be more oriented to the institution's overall management information needs, only one of which is financial.

—Many MIS control function failures have occurred in situations where attempts were made to develop all performance standards and targets before beginning a reporting system. Our recommended strategy is first to develop and obtain general agreement on the reporting framework; then begin to report resource utilization within this framework, even if accepted standards are not yet available; and then to establish and incorporate standards and targets as they are developed.

—There are no generally accepted productivity standards for some functions such as security, social service, engineering, and the like. Our recommendation is that, in such circumstances, it is imperative to adopt some measure of quality. If one then monitors simultaneously resource utilization and quality for a sufficiently long period, the manager will find that either (1) the quality measure is unresponsive to varying levels of resources, or (2) certain relationships between key inputs and outputs can be identified. In the former case, the manager needs a better or more sensitive measure of quality. In the latter he has the basis for objective assessment of the cost/benefits of changes in resource levels, which is the type of information required to establish standards of performance.

—The management information systems of today's hospital must be cost-justified. However, to attempt to do so application by application on a direct cost-replacement basis is to force a disintegrated, inefficient system. Indeed, this kind of "creeping incrementalism" misdirects and obscures the overall goals of an MIS. Cost justification must be carried out within the context for MIS. The plan must be understood by management, periodically updated (perhaps quarterly), and presented in such a fashion that the inevitable conflicts for resources and the ensuing trade-offs of priorities are clear to management.

—In a major institution the MIS function should be guided by a steering committee with wide representation from both resource and program management. The principal activity of such a group would be the approval of the plan and its updates and the assignment of priorities. It should be clear that without a well-understood plan, relative priorities are meaningless.

Conclusion

Some medium- to large-size hospitals are now moving toward a program-resource concept or matrix format. The evolution, recognition, and formulation of the concept will require managers to adopt a systems approach for addressing the special requirements inherent in such an organization.

The basis for decision-making in planning, operations, and control is, of course, adequate and timely information. We feel that a well-developed and implemented MIS is the heart of the systems approach to management.

Newly developed techniques such as program planning and budgeting, zero-base budgeting methods, financial modeling and others must now be understood and utilized by managers if they are to succeed in their job, that is, balancing quality health care delivery with the spiraling costs of such services. It is our contention that use of these and other management science techniques will allow hospital managers to keep pace with inevitable changes.

References

1. Davis, S.: Organizing a Psychiatric Hospital on the Program-Resource Concept, Hosp Comm Psych, February 1970.
2. Neuhauser, D.: The Hospital as A Matrix Organization, Hosp Admin, Fall 1972.
3. Johnson G. V. and Tingey, S.: Matrix Organization: Blueprint of Nursing Care Organization for the '80's, Hosp Hlth Sci Admin, Winter 1976.
4. Pyhrr, P. A.: *Zero-Base Budgeting: A Practical Management Tool for Evaluating Expenses.* Wiley Press, 1973.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

Parkinson's Disease—Overview of Its Current Status

MELVIN D. YAHR, M.D.

Among the various disorders of the nervous system in which Parkinson's symptoms occur, Parkinson's disease is separable as a distinctive clinical entity. Commonly referred to as idiopathic parkinsonism, it is the form most frequently encountered and is distinguishable by: its onset in adult life, usually above fifty years of age; a course which is slowly but relentlessly progressive, leading over a variable period of time to total disability; and a combination of symptoms that include varying degrees of tremor, rigidity and akinesia. Parkinson's disease has been encountered in all races, in every region of the world, and shows no preference for either sex. It is one of the leading causes of neurologic disability in individuals over sixty years of age. Though its exact frequency is unknown, it has been estimated to have a prevalence rate of 100 to 150 per 100,000, with an incidence of 20 cases per 100,000 annually. With the world population showing an increase in numbers of people in the older age groups, Parkinson's disease can be expected to be encountered with increasing frequency in the years to come. To date, attempts to discover its cause and pathogenesis have been unsuccessful. However, advances in our knowledge of the regional biochemistry of the brain, particularly that of the biogenic amines, have made possible a new understanding of this disorder and have established a rational basis for its therapy.

In the many years that have passed since James Parkinson's original description of this disorder (1), numerous studies of its morbid anatomy have been carried out. There is now general agreement among neuropathologists that loss of pigmented neurons, particularly in the substantia nigra, occurs in the brains of those who suffer from Parkinson's disease. The significance of these morphologic changes has become evident since the demonstration that dopamine, a neurotransmitter substance, is found in high concentration in the neostriatum, that is, the caudate nucleus, putamen, and pallidum (2). In Parkinson's disease it is selectively depleted in these structures (3). This depletion of dopamine can be correlated with the degree of degeneration of the substantia nigra—experimentally in animals where such lesions are produced, as well as in the disorder occurring de novo in man. The greater the cell loss in the substantia nigra, the lower the concentration of dopamine in the striatum (4).

In the light of these findings, parkinsonism may now be defined in bio-

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From the Department of Neurology, The Mount Sinai Hospital; and Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Support derived in part from Clinical Center for Research in Parkinson's and Allied Diseases, N.I.H. Grant NS # 11631-01

Requests for reprints should be sent to: Dr. Melvin Yahr, Mount Sinai School of Medicine, Fifth Avenue and 100 Street, New York, N. Y. 10029.

chemical terms as a dopamine-deficiency state resulting from disease or injury to the dopaminergic neuronal system. In the brain, this primarily involves the pigmented neurons of the substantia nigra, which project to the neostriatum. The physiologic role of this system appears to be one of inhibitory modulation of the striatum, which it produces by counterbalancing the excitatory cholinergic activity in this region. Acetylcholine, the neurotransmitter of this latter system, is in abundant supply in the striatum, and its concentration, as far as is known, is unaltered in parkinsonism. In a sense, the situation here may be viewed as analogous to that of acetylcholine and norepinephrine exerting antagonistic actions at sympathetic and parasympathetic nerve endings in the periphery. In the normal healthy state a balance exists between the effects of acetylcholine and dopamine. With loss of the latter in parkinsonism, the balance is disturbed and cholinergic activity predominates. It is as yet not completely certain as to whether the loss of dopamine is the only defect nor that it underlies all of the manifestations of parkinsonism. Indeed, it has been suggested that other neurotransmitters, serotonin, noradrenalin, gamma aminobutyric acid may be primarily or secondarily involved. However, at this point in time, restoration of the striatal dopamine deficiency is the basis for the treatment of Parkinson's disease and appears to have a salutary effect on all its symptoms (5).

Major Clinical Manifestations

The classic triad of symptoms that occurs in this disease is tremor, rigidity, and akinesia. To these one may add others of equal frequency and prominance such as abnormalities of posture, equilibratory disturbance, and autonomic dysfunction. The early symptomatology more often than not is subtle and indeed elusive as to its exact nature or time of onset. Since Parkinson's disease tends to occur in the middle years of life, a sense of slowness or loss of agility of movement, feelings of tremulousness or even depression with its attendant psychomotor retardation, may be attributed to advancing years or the involutional emotional state. It is only when one of the cardinal symptoms becomes evident that the situation becomes clear and the appropriate diagnosis is reached. We have been impressed, as others have, that early manifestations such as infrequent blinking of the eyelids, lack of facial expression, flexed or tilted posture of the trunk, the hesitant rise from a chair in assuming the erect posture, associated with the inability to seat one's self with ease, are early valuable signs present for years before other more obvious symptoms appear. Not infrequently, a poverty of movement with a tendency to maintain positions for unusually long intervals of time in contrast with the normal tendency to shift and be slightly restless when sitting or standing, are other early features. These heralding events all appear to be less well remembered by the patient than the frst instance in which he became cognizant of tremor or difficulty in the use of the limbs for which he sought medical attention. In a review (6) of a large patient population, tremor was the complaining symptom in 70% of patients. However, it was readily obvious on questioning that many could recall one of the above noted ill-defined symptoms being present for years preceding tremor. Indeed all had well-established hallmarks of these other features of the disease at the time of the first examination and in many these features were the major cause of functional impairment rather than the presenting complaint of tremor.

The tremor of parkinsonism has often been described as having very distinctive characteristics. Though some patients do indeed have typical alternating tremor involving thumb and forefinger (pill-rolling), primarily evident at rest with a frequency of 4–7/second, we have been impressed by its variable nature. While its rhythmic alternating nature is a constant characteristic, its rate, amplitude and areas of bodily involvement are hardly so. Tremor of the so-called action variety both postural and intentional of variable frequencies with either minimal or extensive movement of the involved segments of the body is not infrequently encountered. Thought it is more usual for Parkinson's tremor to involve distal segments of the limb, any part of the body may be affected. There is a general tendency for the tremor of parkinsonism once it occurs to spread and involve other segments, but such is not invariably the case. We have encountered many patients whose tremor has remained localized to the initial site of occurrence while other features of the disorder have become more widespread. Tremor is an unsettling symptom to patients because it is such a visible phenomenon and carries with it undesirable connotations as to the emotional stability of the individual. However, it contributes less to the disability of the parkinsonian than the other manifestations of the disease.

Rigidity of the musculature, i.e., resistance to passive movement, is present in almost all cases of Parkinson's disease. Initially, it may exist in a mild degree restricted to a few groups of muscles but invariably it progresses to involve more areas of the body. In its early stages when not readily obtainable by passive movements of a limb, it can be induced by having the patient carry out active synkinetic movement of the contralateral limb. Rigidity contributes to the limited range and slowness of movement which characterizes Parkinson's disease but less so than akinesia. It also, to a limited extent, is a cause of the sense of muscle weakness which many patients experience. This latter symptom, however, is usually more apparent than real for in fact the parkinsonian patient can usually carry out an initial forceful contraction but is unable to maintain or do so repetitively. Rigidity has also been implicated as a cause of the postural deformities of limbs and trunk which are so characteristic and frequently encountered. Conceivably the sustained forceful contraction of rigid muscles can produce such abnormalities. However, their early occurrence in parkinsonism when rigidity is barely demonstrable and their experimental production in animals without rigidity in whom the nigro-striatal pathway is interrupted, suggest that it is a symptom in its own right. Indeed accumulated evidence would indicate that striatal imbalance resulting from dopamine deficiency underlies the postural abnormalities.

The body posture of the individual with established Parkinson's disease is characteristic and readily recognizable. In the erect position the head is bowed, the trunk bent forward, the shoulders drooped, and the arms flexed at the elbows with hands held in front of the body and the knees assume a flexed posture. The totality of this appearance is that of an individual whose body is immobilized in an anteriorly shifted overhanging position. Indeed the center of gravity for the parkinsonian appears to be displaced forward leading to his inability to stand erect without toppling and a tendency to be propulsive when walking. The small-stepped festinating gait of the parkinsonian is a distinctive feature and results from a combination of akinesia, rigidity and this postural abnormality. Postural abnormalities less profound can be detected in the early stages of parkinsonism. The most common are seen in the upper limbs. A tendency for the hand to assume an ulnar deviated position with flexion of the fingers at the metacarpal phalangeal joints, the so-called "striatal hand" is often encountered. Tilting of the trunk usually to the side opposite that of initial limb involvement and equinovarus posture of the foot are other postural abnormalities.

One of the most disabling features of Parkinson's disease that bedevils the patient more than any other is the inability to initiate, maintain and perform with rapidity and ease volitional motor activities of the most ordinary sort. This contributes more to the disability of this disorder than any other symptom. The terms bradykinesia, hypokinesia, and akinesia aptly describe the degrees of impaired movement which occur without any disturbance in muscle power, coordination or presence of rigidity. In all the acts of daily living the patient is conscious of delay in execution which at times may reach a total standstill. A meal normally consumed in twenty minutes may be only half eaten by a parkinsonian in an hour or more. Dressing and washing may require the better part of a morning and walking may be interrupted by the patient coming to a complete halt and being "frozen" in place. The poverty of movement which results from the bradykinetic and akinetic state is apparent in a broad variety of reflex motor activities normally occurring with little or no conscious awareness. Periodic eyeblinking; mimetic facial movements; associated movements of the arms when walking; shifting of weight when standing or sitting; assuming a relaxed posture when sitting are all impaired and rarely occur except with conscious effort. In fact, the parkinson patient is under constant stress to voluntarily perform actions which in prior days came naturally and involuntarily. Akinetic mechanisms play a role in the voice disturbance, namely, its reduced amplitude and monotonous quality; in the disorder of gait which, in addition to its shuffling nature, is difficult to start, maintain or alter in tempo on command; and in use of the upper limbs especially in writing. With advancing akinesia parkinsonians can rarely maintain the continuous motor activity required in script writing and resort to printing individual letters. The capricious nature of akinesia adds greatly to the misery which the parkinsonian patient experiences. Its intermittent paradoxical nature leads to accusatory remarks by those involved in his daily care regarding the patient's motivation and sense of dependency. The literature on parkinsonism is replete with descriptions of patients who though totally immobile and in need of assistance for any and every act will suddenly rise and move normally for a period of time; the so-called paradoxical akinetic reaction. Family members, nurses and attendants are prone to state "he can do it when he wants to, five minutes ago he couldn't move a muscle now he is able to do anything he wants," as if the phenomenon were willed or strictly a matter of motivational nature. Undoubtedly, psychological factors play a role in chronic illness and Parkinson's disease is no exception but this profound disturbance in motor activity without question is primarily based on organic neural factors involving the integrative functions of the nervous system at a very high level.

A variety of symptoms referable to autonomic dysfunction are encountered in Parkinson's disease. These consist of thermal paresthesias undoubtedly related to alterations in vasomotor control of peripheral blood vessels; hyperhydroses indicating overactivity of sweat gland innervation and a tendency to hypotension with poor baroreceptor mechanisms leading in some instances to orthostatic syncopy. Skin changes with eczematous eruption especially over the forehead and sialorrhea are not fully explained as to mechanism and may not be a direct expression of autonomic dysfunction. More likely they relate to the attendant difficulties in personal hygiene.

Considerable comment has been made regarding the intellectual capacity of those with Parkinson's disease. There are some who feel that dementia is an intrinsic characteristic of the disease increasing in severity as it progresses (7). Others have implied that intellectual deterioration occurs in those with specific manifestation of the disease, particularly akinesia (8). Contrary to these reports are those that contend, as did James Parkinson, that the senses are unaffected. In our own observations in which testing has been carried out so that motor activities play a minor role in their performance and hence akinetic and rigid aspects of the disease are not a factor, we have found a number of cognitive, perceptual and memory deficits (10). To some extent the cognitive and perceptual deficits relate to cerebral dominance in that those with minor hemisphere involvement were more seriously affected (11). These findings suggest that the striatum plays a role in cerebral dominance in addition to the cerebral cortex. Memory deficits encountered in Parkinson's disease were not of a major degree. It would appear from these findings that there is an element of intellectual loss but not one of major proportions nor is it an outstanding characteristic of this disease.

Etiologic Considerations

Though a variety of agents including toxic and infective have as a result of their involvement of the nervous system induced parkinsonism, the cause of Parkinson's disease remains unknown. Some have suggested that genetic factors play a role, others that viral agents are the cause or that an enzymatic defect is acquired as part of the aging process which specifically affects the monoaminergic cells of the nervous system or in more generalized fashion.

Support for a genetic basis is primarily derived from family studies in which historical documentation is brought forward indicating that 5–15% of family members may suffer from the disease (12). Critical analysis of such data in which careful study of the purported involvement of family members is carried out fails to show that the expected incidence of Parkinson's disease in such instances, is above that found in controls (13). Leaving aside the controversy still present in this regard, there is general agreement that if inheritance does play a role it is not dominant nor does it fit a monogenic model. Whether it fits some polygenic model is open to question.

Considerable effort during recent years has been made to relate Parkinson's disease to the epidemic of encephalitis lethargica (von Economos) which occurred from 1918 to 1926 (14). In retrospective analysis of age of onset of symptoms of parkinsonism, supporters of this concept point to a cohort who have been aging together and in whom the date of onset of their parkinsonism has been rising by one year for each calendar year (15). Based on this data, they have proposed that Parkinson's disease is postencephalitic and a late consequence of subclinical infection with the virus of encephalitis lethargica. The inferences drawn from these data are that there is a single etiology for all parkinsonism and that a sharp decline in its incidence can be expected in the coming decades when those at risk have died off (16). Indeed a virtual disappearance of Parkinson's disease is predicted by the end of this century. Leaving aside the methodologic objections used in collecting and analyzing these data and alternate explanations for its occurrence (17), pathologic, clinical, and immunologic findings indicate that postencephalitic Parkinson's and Parkinson's disease are very separate entities (18, 19). The former, though affecting the substantia nigra, produced other widespread changes in the nervous system and is characterized by neurofibrillary changes and the absence of Lewy body formation. Recent studies of the immunologic properties of postencephalitic brains reveal antigenic sites which bind with Influenza A virus. No such sites are found in the brains of patients with Parkinson's disease (20). Clinically, postencephalitic parkinsonism has certain distinctive features such as oculogyric crises that do not occur in Parkinson's disease. Lastly, the response to therapeutic agents varies considerably. While postencephalitics are most tolerant to anticholinergic agents, they can only tolerate limited amounts of levodopa (21). It appears to this author that it is an error to formulate a unitary etiologic hypothesis for these two types of parkinsonism. One would be equally in error to exclude the possibility that some type of viral infection, presumably of the "slow virus" variety, may well underly Parkinson's disease. However, if it does, it is highly unlikely that it is the same agent that caused encephalitis lethargica and its sequelae.

Since the demonstration that striatal monoamines, particularly dopamine, are decreased in all forms of parkinsonism, attention has centered on its role in the etiogenesis of Parkinson's disease. Conceivably this loss, rather than being secondary to degeneration of cells responsible for its production, could result from a primary defect in its metabolism. In regard to the latter, it is of some import that the therapeutic response in Parkinson's disease which results from levodopa cannot be obtained with L-tyrosine, its immediate precursor. Since this reaction is dependent on tyrosine hydroxylase, the question arises as to whether there is a deficiency of this enzyme. To date isolation of this enzyme from Parkinson's brains nor determinations as to whether its activity is normal have not been satisfactorily accomplished. Assuming its activity is below normal, the mechanism by which it occurs is yet to be elucidated. However, since parkinsonism is, in a sense, age-specific in onset, making its appearance in the latter years of life, it might result from mechanisms related to aging of neuronal cells, and in individuals in whom nigral cells are particularly vulnerable to such effects. Such vulnerability might be multifactoral in origin and relate to any one of a number of mechanisms, i.e., genetic, viral or toxic. It should be readily apparent from this discussion that as of this writing the cause of Parkinson's disease is as much a mystery today as it was a century and a half ago when James Parkinson wrote his now classic monograph. However, what has changed remarkably in these many years is the investigative interest of scientists from numerous disciplines in this disorder. To a considerable extent, this arose from the dramatic therapeutic response obtained with the use of levodopa. The pharmacologic effects of this agent on the brain, when used judiciously, has allowed for extended periods of time in a large proportion of patients.

Therapeutic Considerations

There is at present a consensus among neurologists that levodopa administered alone or in combination with a peripheral dopa decarboxylase inhibitor is the treatment of choice for Parkinson's disease. However, less than complete agreement exists as to when best to initiate treatment; whether or not its beneficial effects are sustained after long-term administration; and more importantly, its impact on the natural history of the disorder, particularly the progressive disabling nature.

As is often the case in a chronic disease of unknown etiology with protean manifestations and no curative therapy, hard and fast rules regarding treatment, when applied indiscriminately to all patients, give less than optimal results. Indeed we have found it wise in Parkinson's disease to highly personalize treatment programs using as a guide, not only the patient's symptomatology, but the degree of functional impairment and the expected benefits and risks obtainable from presently available therapeutic agents. In those instances of Parkinson's disease where symptoms are minimal and the functional capacity unimpaired, simple measures such as reassurance and use of anticholinergic agents in limited dosage often suffice. Levodopa is best reserved for use when symptoms develop which interfere with employment, social obligations, daily activities of living, etc. There is no evidence at the present time that early use of any form of therapy in any way alters the underlying pathologic process of this disease (22). It has, however, been reported (23), that the death rate in parkinsonism during the first 5 years of the disease is diminished by the early use of levodopa. We have recently reviewed our own experience with this agent in patients in treatment for time periods up to 7 years (Yahr, unpublished data presented at the International Symposium on Parkinson's Disease, London 1974). These data reveal that levodopa has a sustained effect on parkinson symptoms, but is most beneficial during its first 3 years of use. Subsequently, there is some fall-off in clinical efficacy primarily related to increasing side effects and a tendency to a more uneven therapeutic response; the so-called "on-off" response (24). Progression of the disease occurs while on levodopa, as evidenced by the development of additional signs of the disorder which readily can be demonstrated when treatment is temporarily discontinued. The major impact of levodopa therapy is apparent in the improved quality of life for the parkinsonian. Patients utilizing this agent remain functional for longer intervals of time and do not suffer the degree of incapacity and dependence that previously characterized this disease. There is a striking extension of the period in which patients lead a more useful and independent existence. In regard to life expectancy, an increase of 1.5 years was found when this group was matched with one studied prior to the introduction of levodopa (6). Survival however, was not uniform for all age groups. Younger patients, that is those under 55 years of age, showed no lowering in death rate while it had decreased for those over 70 years. Except for those in the end stages of the disease, no correlation could be found as to the severity of involvement prior to treatment and the eventual therapeutic outcome. These data reinforce our therapeutic concept, that a total assessment of the individual needs of a given patient, should be the prime determinant in recommending one or another type of therapy. At present levodopa, though far from being the ideal antiparkinson agent, is the best available. Its judicious use effectively benefits a large proportion of those suffering from Parkinson's disease.

References

1. Parkinson, J.: *An Essay on the Shaking Palsy*. Sherwood, Neely and Jones, London, 1817.
2. Bertler, A. and Rosengren, E.: Experientia, 15:10, 1959.
3. Hornykiewicz, O.: In *Biochemistry and Pharmacology of the Basal Ganglia*, p. 171. Edited by E. Costa, L. J. Cote and M. D. Yahr. Raven Press, Hewlett, N.Y., 1966.
4. Bernheimer, H., Birkmayer, W., Hornykiewicz, O., Jellinger, K. and Seitelberger, F.: J Neurolog Sci 20:415, 1973.
5. Yahr, M. D., Duvoisin, R. C., Schear, M. J., Barrett, R. E., and Hoehn, M. M.: Arch Neurol 21:343, 1969.
6. Hoehn, M. M. and Yahr, M. D.: Neurology (Minneapolis) 17:427, 1967.
7. Pollack, M. and Hornabrook, R. W.: Brain, 89:429, 1966.
8. Garron, D. C., Klawans, H. L., and Narin, F.: J Nerv Ment Dis 154:445, 1972.
9. Bwen, F. P., Hoehn, M. M., and Yahr, M. D.: Neuropsychologia, 10:355, 1972.
10. Bowen, F. P., Brady, E. M., and Yahr, M. D.: In: *Parkinson's Disease: Rigidity, Akinesia, Behavior, Vol. 2*, p. 315. Edited by J. Siegfried. Hans Huber, Berne, 1972.
11. Bowen, F. P., Hoehn, M. M., and Yahr, M. D.: Neurology (Minneapolis) 22:32, 1972.
12. Martin, W. E., Youg, W. I., and Anderson, V. E.: Brain, 96:495, 1973.
13. Duvoisin, R. C., Gearing, F. R., Schweitzer, M. D., and Yahr, M. D.: In *Progress in Neurogenetics, Vol. 1*, p. 492. Excerpta Medica, Amsterdam, 1969.
14. Poskanzer, D. C. and Schwab, R. S.: J Chron Dis 16:961, 1963.
15. Brown, E. L. and Knox, E. G.: The Lancet 1:974, 1972.
16. Poskanzer, D. C., Schwab, R. S., and Fraser, D. W.: In *Third Symposium on Parkinson's Disease*, p. 8. Edited by F. J. Gillingham and J. M. L. Donaldson. Livingstone, Edinburgh, 1969.
17. Duvoisin, R. C. and Yahr, M. D.: Neurology (Minneapolis) 22:32, 1972.
18. Duvoisin, R. C. and Yahr, M. D.: Arch Neurol 12:227, 1965.

19. Stadlan, E. M., Duvoisin, R., and Yahr, M.: In *Proceedings of the Fifth International Congress of Neuropathology*, p. 569. Excerpta Medica International Congress Series, 1965.
20. Gamboa, E. T., Wolf, A., Yahr, M. D., Harter, D. H., Duffy, P. E., Barden, H., and Hsu, K. C.: Arch Neurol 31:228, 1974.
21. Duvoisin, R. C., Antunes, J. L., and Yahr, M. D.: J Neurol Neurosurg Psychiat . 35:487, 1972.
22. Yahr, M. D., Wolf, H., Antunes, J. L., Miyoshi, D., and Duffy, P.: Neurology 22 (Pt. 2):56, 1972.
23. Birkmayer, W.: In *Current Concepts in the Treatment of Parkinsonism* p. 141. Edited by M. D. Yahr. Raven Press, New York, 1974.
24. Yahr, M. D.: Adv Neurol 5:397, 1974.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

The Role of Television in Continuing Education

CARTER L. MARSHALL, M.D. AND RODNEY ALEXANDER, M.P.A.

Abstract

In the last two decades, eighteen CME (continuing medical education) projects utilizing television have been described in the literature. Scrutiny of these reveals that, although the authors were almost always positive, none of the projects was adequately evaluated, the size and nature of the physician audience were difficult to ascertain, and efforts to make physicians aware of the programming were poorly carried out. As a group, the projects were mounted without much attention to what could be learned from them and as a result we know too little about the benefits of television to use it optimally, and too little about its drawbacks to avoid them. It is suggested that television is best regarded as a tool to create awareness and generate interest in CME rather than as an independent educational approach. Broadcast television of CME suffers from lack of concurrent feedback and little is known about the relationship between effect and duration of exposure. Rigorous research is needed to maximize the utility of television in CME.

The legislation of mandatory continuing education requirements by state legislatures and the rise of CME (continuing medical education) requirements for membership in professional societies make necessary the development of educational modalities that are accessible and appropriate for physicians in private practice. Hospital-based CME is generally not convenient for the community-based physician and is particularly inappropriate when built around audits of patient records. A number of attempts to solve the problem of access have been mounted over the years utilizing broadcast television. In the last two decades, eighteen of these CME projects utilizing television have been described in the literature. A review of these articles indicates that these efforts have met with marginal success in attracting an audience and little is known about their influence on physician behavior. Even though some programs remained in operation for several years, they have not been able to mold the television medium into an important instrument for postgraduate medical education. This paper reviews and comments on the eighteen television-based continuing educational programs described in the literature between 1954 and 1974.

The target audience of television-based CME has invariably been the

From the Center for Continuous Education, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029. (Both authors are now at Morehouse College, Medical Education Program, Box 86, Atlanta, Ga. 30314.)

primary care physician, i.e., general practitioners, pediatricians and internists. None of the articles reviewed indicated a specific interest in attracting physicians from other specialties, although one series directed its efforts in part to attracting nurse and other allied health personnel (1). Another sought to interest the lay public as a means of stimulating more physician interest in continuing education (2). With the exception of the original University of Utah series which used a local NBC affiliate, all subsequent television-based continuing medical education in the United States have employed the facilities of nearby Educational Television Stations (ETV). Applications in Canada and Britain have, of course, used the facilities of the Canadian Broadcasting Company (CBC) and the British Broadcasting Company (BBC).

Typically programs have varied in length between 20 minutes and one hour. They were aired weekly either before or after the regularly scheduled programming of the station. Ten articles gave no clear indication whether programming was live, or prerecorded on film or videotape. Of the eight that did, three were live, three prerecorded, and two employed both production modes. Educational formats were even more difficult to determine; mention was made of lectures, panel discussion, "seminars" and grand rounds, but no particular format seemed to predominate. Beyond the fact that the CME television programs seemed to attract the general practitioners and primary care specialists for whom they were intended, little is certain about the viewing physician. Warner found that more physician viewers lived in rural areas than non-viewers (3). However several years later, Castle found no urban-rural differences (4) while Denne et al reported a preponderance of urban viewers over rural viewers (5). Interestingly enough, all three of these studies were done in Utah. McGuiness found that among general practitioner viewers, most were foreign medical graduates (6). He also found viewing to be more prevalent among physicians affiliated with "better hospitals" and those who were over 43 years of age (7).

Differences in the manner of reporting audience size makes it difficult to compare the extent to which potential audiences were successfully reached. Some authors reported audience size on the basis of an "average per program" (2, 7–9). More reported the percentage of the physician population viewing at least one program (4–7, 9–13) and others did not report at all (1, 14, 15). As a means of gauging success, average audience size is probably superior to the percentage of physicians who viewed at least one program because the latter may be inflated by a sizable number of physicians who watched once and only once. In Montreal, for example, Vaillancourt et al reported average audience size as 22%; yet 64% of physicians had watched at least one program (9). Average audience size range from a low of 3.6% for the New York Academy of Medicine sponsored series in 1963, to a high of 30.6% in the Maine series. Physicians who watched at least one program ranged from a low 5.6% in New York to a high of 80% in Hamilton, Canada. These wide variations on reported audience sizes and the persistency of low viewership generally, may be accounted for by the subject matter and the quality of presentation of programming as well as other program characteristics such as time of scheduling. Others factors of importance would include the extent to which advance publicity, if any, reaches the practitioner and the availability and popularity of alternate sources of continuing education.

Our review of the literature makes it clear that these factors are impossible to assess from what has been written. There is no way of comparing the content or quality of programming produced by the various projects based on the available literature. While it is reasonable to assume that such differences existed and that these differences affected audience size, it is impossible to be more specific. For example, the reputation of physicians who participate in programs may also account for variations in audience size. Although not explicitly indicated, it is clear that physicians were asked to participate in programs largely because of their expertise in the subject area under discussion. However, in our experience many doctors are uncomfortable in front of cameras and few display a natural television "presence." Restricted time of physicians, lack of interest, and the need to deal with many topics severely limit the opportunity to work with any one physician to help improve his delivery. The viewer who is attracted by a high quality reputation may be driven from the small screen by low quality delivery.

The scheduling of programs for broadcast and the extent to which sponsors publicized the availability of CME programming are factors of great importance. Only one of the articles reviewed (16) indicated experimentation with the times programs were shown, although in some cases programming was shown twice at different times of the day (5, 11, 13). Projects for which we have information were almost always scheduled between 9 PM and 8 AM (3, 5–13). In at least five cases, these programs were scheduled just before or just after regular programming (3, 4, 8, 10, 11). In only one case was it indicated that CME programming was part of the channel's regular production effort (2). By scheduling programming during late evening program hours, sponsors minimized costs, avoided disruption of regularly scheduled programming, and no doubt avoided thousands of potential lay viewers. In a few cases the end of the regular program schedule and the beginning of medical programming were separated by five minutes of "dead air" or a test pattern (4, 8, 10, 13). The presumption was that a nonphysician watching the channel would assume that activities had ceased for the day. It is not clear how many physicians may have reached the same conclusion.

The stress placed on restricting lay viewers reflected wide concern over a related problem: adverse public reaction to television presentation of explicit medical material. To avoid adverse reaction and "protect" lay viewers, a few institutions went to the trouble of transmitting a scrambled signal which the recipient institution unscrambled with a special decoder (1, 14, 17). In this case the physician was requested to watch at a hospital in which he had privileges. He could not unscramble the signal in his home. Although restricted programming was said to permit greater freedom of discussion and a wider range of topics, one writer felt that the true reason for restriction was to prevent the physician participant from augmenting his own practice by enhancing his public image as an expert (14). Interestingly enough, there is no evidence of substantial lay interest in such programs. McGuiness claims that the reason for this is that " . . . most scientific medical programs are just too technical in nature to permit sustained attention and interest on the part of the lay public" (7). Out of the 101 programs sponsored by his organization, only two generated comments, and both of these were requests for transcripts (7). Warner and Bowers estimated lay viewing to be 0.8%, and Hunter estimated one lay viewer for every 20 physicians (13). Cameron, in his query to 1108 physicians, obtained only 29 persons who consulted the physician after watching one or several programs.

While much attention was devoted to minimizing adverse public reaction and avoiding lay viewers, little attention was paid to alerting the practitioner population to the existence of televised CME. The importance of advertising in securing audiences for commercial television programs is axiomatic. In addition, journal advertising and mailed fliers are an integral part of traditional continuing education courses throughout the United States. In spite of this, half of the articles reviewed failed to make any mention of how or whether physicians were notified of the availability of such programming (3, 6, 7, 12, 16, 18, 19). Remarkably, only five of the projects notified potential viewers through the familiar mailings to physicians homes and office or through announcements in medical publications (4, 5, 10, 11, 13). In only two instances were special efforts made to increase audience size through specially designed notification techniques (8, 15).

Robertson et al, in an attempt to achieve more than "the usual 10–20% of the potential audience, reported that "attention-getting" mailings were devised and sent to all physicians in Maine. Other information on individual programs along with a three-ring notebook with the name of the series (Boston Medical Reports) imprinted on it was also sent to physicians. In that way summary information on programming could be maintained in the notebook for easy reference. How successful these efforts were is not clear, although the authors claimed to have built a 30% average viewing audience (8), the highest recorded.

In Alabama, Crevasse reported that specific reminders such as telephone calls to a group of physicians could account for as much as a 35–40% difference in response rate (viewing) when compared with a control group receiving no reminders. Unfortunately, no information on average viewing audience was presented. Further evidence on the potential effects of publicity and the use of "reminders" is seen in a number of physicians who said they did not watch because they "were doing other things" or they "forgot." Castle (4) reported similar findings as did Fahs (12) and Meighan et al (10).

A number of attempts were made to assess the educational impact CME programming (1, 3, 14, 11, 12, 18). While these results were generally positive, they were based exclusively on physician testimony or on pre- and post-measures of knowledge. Only one study was designed to objectively measure

TABLE I

Summary of Eighteen Television-Based Continuing Education Projects

Ref.	Time span	Institution	Urban	Rural	Publicity	Evaluation	Conclusion
3	10/53–12/53	University of Utah College of Medicine	X	X	?	4 Programs	Broadcast television is particularly effective for rural physicians.
4	9/59–4/62	University of Utah Medical College	X	X	Mail	4 Programs	Open-circuit television can be used without significant undesirable effects.
14	3/61–1/63	Jacksonville Hospitals Educational Program*	X		?	None	Use of scrambling devices is "highly desirable" for postgraduate medical education.
6	1/63–12/65	New York Academy of Medicine	X		?	8 Programs	Program effectiveness depends on content, technical intricacy, extent to which program deals with concrete "bread and butter" issues.
7	1/63–12/65	New York Academy of Medicine	X		?	4 Programs	See above
18	1/63–12/65	New York Academy of Medicine	X		?	4 Programs	See above
16	1/63–12/65	New York Academy of Medicine	X		?	4 Programs	See above
8	3/64–6/64	Massachusetts Medical Society et al	X	X		12 Programs	Sufficiently large and interested audience attained to warrant a second series.
10	1/66–4/66	Oregon Medical Association	X	X	Mail and county medical bulletins	14 Programs	Participation by physician learners depends on sound principles of education and an appropriate organizational structure.
11	1/66–6/66	Asso. for the Study of Medical Education (Eng.)	X		Mail and Medical Press	6 Programs	Programs well received by public, some indication that learning resulted among viewers.
7	1/67–6/67	Faculty of Medicine University of Montreal	X		?	6 Programs	Findings suggest that general practitioners in rural area are "quite interested" in CME television. Presentation of more material and more publicity needed for success.

17	1/63–12/65	University of Southern California School of Medicine et al*	X		Unspecified promotional materials	30 Programs	Further evaluation will be conducted in future.
1	(2 Years)	The University of California School of Medicine et al	X		?	1 Program	Because of "serious sample depletion" no "measurable" behavior or information changes attributable to TV programming obtained. Worthiness of programs remains moot question.
12	1965–1968	Minn. State Medical Association, et al	X	X	?	9 Programs	CME through television has much potential, however, realization may require assistance of professional broadcasters, clearer statement of educational objectives and more effective advertising. More imaginative planning such as use of open telephone line for immediate feedback may also be necessary.
15	Not indicated	Not indicated (Alabama)	"Semi-rural"		Mail, telephone	3 Programs	Use of special direct mailings and telephone calls with invitation to participate in program evaluation can increase audience size significantly.
13	1967–1968	Faculty of Medicine University of Western Ontario	X		?	3 Programs	Television used for CME can be "effective in transmitting new medical instruction that will be retained at least several months."
5	(11 Years—1959–1970?)	Regional Med. Program and University of Utah	X	X	?	8 Programs	Adequate motivation of learner requires his involvement in educational experience. Broadcast television does not provide for this. There is doubt that open-circuit television can compete with other means of continuing medical education and commercial television.
2	1968–1970	Faculty of Medicine McMaster University & Hamilton Academy of Medicine (Canada)	X	X	Advertised as part of station's regular programming	†	Possible to produce CME programs of quality on large scale. Felt goals of reaching "reasonable number of MD's with fairly acceptable CME" satisfied.

* Interinstitutional links; scrambled signal used.

† 41 programs produced by other universities and institutions.

the impact of programming on physician behavior. Mostly this effort failed because of "serious sample depletion" (1). The attempt intended an audit of patient records to determine the effect of programming on the use of steroids. Not surprisingly, too many of the records were either unavailable or too poorly maintained to be of use.

Discussion

Table I summarizes the eighteen projects and the conclusions drawn by authors. In addition to what has already been said, it is worth noting that with one exception, the projects are favorably described by the authors. This in spite of the very limited nature of attempted evaluations, the lack of information about the size and nature of the viewing audience, and the geneal lack of advanced publicity about the programs. It seems to us that after more than twenty years of experience using television for CME we are left with a series of impressions unsubstantiated by well-designed research. In our view, the overall experience with television has been a negative one in that we know too little about the benefits of television to use it optimally and too little about its drawbacks to avoid them.

Attempts to employ television in other health-related ways have been similarly disappointing. Seidenfeld (19), O'Keefe (20), and Robertson et al (21) have sought to use television in educating the public on health matters and none have been satisfied with the results. On the other hand, the success of traditional CME in altering physician behavior is so limited that it is perhaps inappropriate to expect more from television. In the absence of a standard of success, it is difficult to estimate the degree of television's failure.

After five years of experience with medical uses of television, it is our belief that the single great failing of previous CME projects is the lack of a theoretical construct through which the diverse data can be logically integrated. In our own work we have been guided by Lazer and Bell (22) and by Beal and Bohlen (23) who pointed out that while mass media (television, radio, most newspapers) create awareness and generate interest, the evaluation and adoption of new ideas is influenced primarily by peers, friends, or expert sources such as books or periodicals. This means in effect that television is a general medium. This in turn is probably related to the basic defect of television, the absence of concurrent audience feedback. Without such feedback, improvements in format and presentation are possible only after retrospective assessment. Another difficulty lies in the fact that so very little is known about the relationships between the duration of exposure and the desired effect. This dose-duration-effect problem cannot be solved by development of concurrent feedback mechanisms alone because presumably the optimal dose-duration relationship would generate different feedback from a suboptimal one and without a clear idea of optimal dose-duration it is not possible to know with certainty what favorable or negative feedback represents. In short, feedback is dose specific and duration specific.

We would suggest that given the present state of knowledge about television, broadcast television as a total in CME is best regarded as an advertisement. By this we mean that since its impact is relatively superficial, television presentations should be designed to encourage the viewer physician to seek additional information either from print sources available through the sponsor of the television broadcast or from attendance at a traditional CME course on the subject offered concurrent with the television broadcasts. For example, we would reverse Robertson's approach of supplementing video material with loose leaf summaries. Our feeling is that television should introduce, summarize, or present a case; the detailed material is better left to print media or to traditional course structure.

Our belief is that the television broadcast should be repetitious because it is intended to call attention to available CME material or courses by introducing the subject. In other words, television is aiming a superficial message at a wide audience and there is no need to attempt to provide the detailed, in-depth information offered through the concurrent mail-order face-to-face course. There are two other alternate approaches which seem appropriate to television but neither is presently suitable for braodcasting. One is taped or live material presented to an audience by an instructor who is with the audience at the time of the presentation. The other is the live presentation of material to an audience that can interact with a remote instructor through a bidirectional audio hookup. In all cases, television supplements but does not dominate the presentation. Instead it holds audience interest while the instructor remains responsible for transmission of the detailed information. The basic idea here is that television should not be regarded as an educational instrument sufficient unto itself.

Unfortunately, advocating a superficial and secondary role for television in CME does not identify the format and presentation best suited to this purpose. Doing so is extremely important. While television is not the Triptolemus of CME, its capacity to disseminate important if superficial information should not be ignored at a time when CME requirements for relicensure and recertification are proliferating. In addition, as mentioned earlier, the potential benefits and utility of television remain largely unexplored. The need for rigorous research is obvious. Such research, we feel, should be both formative and summative. The former could be conducted as an integral part of ongoing CME courses using television supplements. A device known as a split cable enables a divided audience to watch the same channel simultaneously and see different programming.* By randomly assigning course enrollees into two groups, programs can be modified and "fine tuned" to determine optimum physician receptivity and response to various formats and presentations. Summative research is badly needed in CME generally and is in no way restricted only to CME using television. However difficult and expensive, randomized clinical trials comparing television-supplemented CME to other types of presentation would begin to define the effectiveness of CME with and without television and eventually throw some light on various television formats (live with bidirectional audio or tape with instructor present, etc.). One would hope that in this research the several modalities would be assessed in terms of physician behavior rather than test scores or physician preference. Ultimately, the appropriate use of television should be defined through research, including research scrutiny of the approach outlined in this paper.

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* Developed by Edward Wallerstein who is associated with the Center.

References

1. Mock, R. L., McCoard, B. F., et al: Northern California Post-Graduate Medical Television: An Evaluation, 45:40–46, 1970.
2. Smith, S. L., Barrows, H. S. et al: Physician and Public Interest in Medical Television Broadcasts: A Report on Two Years Experience, Can Med J 104:1101–1103, 1974.
3. Warner, R. S., and Bowers, J. Z.: The Use of Open Channel Television in Postgraduate Medical Education, J Med Educ 29:27–35, 1954.
4. Castle, C. H.: Open Circuit Television in Postgraduate Medical Education, J Med Educ 38:254–260, 1963.
5. Denne, K. T., Schorow, M., et al: Mass Communication Media in Continuing Education, J Med Educ 47:712–716, 1972.
6. McGuiness, A. C., Menzel, H., et al: Continuation Medical Education by Open-Circuit Television: A Preliminary Report, J Med Educ 39:735–745, 1964.
7. McGuiness, A. C.: The New York Academy of Medicine TV-PG Efforts in a Metropolis, J Med Educ 40:878–881, 1965.
8. Robertson, G. J., Pyke, H. F., et al: A Post-Graduate Educational Television Series for Practicing Physicians in the State of Maine—A Preliminary Review and Report of Initial Education, J Maine Med Ass 56:41–43, 1965.
9. deVaillancourt, G. and Gill, M.: Continuing Medical Education by Television—A Canadian Experience, Can Med Assoc J 98:1136–1139, 1968.
10. Meighan, S. S. and Tresder, A: Continuing Medical Education Through Television—The Oregon Experiment, JAMA 200:762–766, 1966.
11. Cameron, J. S.: Broadcast Television for Doctors—A First Evaluation, Br Med J 1:911–914, 1966.
12. Fahs, I. J., and Miller, W. R.: Continuing Medical Education and Educational Television: An Evaluation of a Series for Physicians in Minnesota, J Med Educ 45:578–585, 1970.
13. Hunter, A. T., and Portis, B.: Medical Educational Television Survey, J Med Educ 47:57–63, 1972.
14. Michael, M.: Television in Graduate and Post-Graduate Medical Education, J Med Educ 38:261–263.
15. Crevasse, L.: The Wizardry of Television—Or Is It? Alabama J Med Sci 7:201–202, 1970.
16. Menzel, H., Maurice, R., et al: The Effectiveness of the Televised Clinical Science Seminars of the New York Academy of Medicine, Bull NY Acad Med 42:679–714, 1966.
17. Brayton, D., Smart, C. R., et al: The Medical Television Network: A Progress Report on A Scrambled Broadcast System for Continuing Medical Education, J Med Educ 43:1011–1017, 1968.
18. Menzel, H., Maurice, R., et al: Evaluation of the New York Academy of Medicine's Television Programs, J Med Educ 41:826–843, 1966.
19. Reported in Bauer, R.: The Obstinate Audience, Amer Psychol 19:319–328, March 1964.
20. O'Keefe, M.: The Anti-Smoking Commercials: A Study of Television's Impact on Behavior, Pub Opinion Quart 35:242–248, Summer 1971.

21. Robertson, L., Kelly, A., et al: A Controlled Study of the Effect of Television Messages on Safety Belt Use, Amer Health 64:1071–1080, November 1974.
22. Lazer, W. and Bell, W.: The Communications Process and Innovation, J Advert Res 6:2–7, September 1966.
23. Beal, G. and Bohlen, J.: The Diffusion Process Special Report No. 18, Agricultural Extension Service, Iowa State College, Ames, Ia. 1957.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

Primary Cesarean Section in the Multipara: 1971–1974

REBECCA NACHAMIE, M.D., AUGUSTO CASTRO-MARIN, M.D., JASMIN MOSHIRPUR, M.D., DAVID SCHONHOLZ, M.D., AND S. B. GUSBERG, M.D.

Abstract

From 1971–1974 there were 9,119 deliveries at the City Hospital Center At Elmhurst. Of these, 8.2% were cesarean sections. The primary cesarean sections in multiparous patients are analyzed. They represented 52.5% of all primary cesarean sections. Cephalo-pelvic disproportion was a predominant indication for primary cesarean sections in multiparous patients, as it is in primiparous patients. Maternal and fetal morbidity and mortality are improved when the need for primary cesarean section in the multipara is evaluated early in pregnancy and labor and acted upon.

This report is a review of the primary cesarean sections performed upon the multiparous patient at the City Hospital Center at Elmhurst from 1971–1974. It is our intent to emphasize the frequency with which the primary cesarean section is necessary in patients who have previously successfully delivered vaginally. We enumerate the fetal and maternal indications. It is clear that many of these situations cannot be eradicated. This study is intended to improve maternal and fetal outcome by reviewing, and thus reemphasizing, the well-recognized situations necessitating primary cesarean section whether in the primipara or multipara. We cannot be complacent regarding the delivery of the multiparous patient.

Study Population

The department of Obstetrics and Gynecology of the City Hospital Center at Elmhurst is a division of the Department of Obstetrics and Gynecology of the Mount Sinai School of Medicine and as such is staffed by the same resident and attending physicians. The group under study includes the deliveries from 1971 through 1974 at the City Hospital Center at Elmhurst. As listed in Tables IA and IB there were 1801 deliveries in 1971, of which 138 or 7.7% were cesarean sections and the remainder were vaginal deliveries. The total number of primary cesarean sections in that year was 88, or 4.9% of all deliveries; whereas 50 were repeat cesarean sections. Of the 88 primary cesarean sections, 55 were performed on primiparous patients and 33 were performed on multiparous patients. Tables IA and IB also list the equivalent statistics for 1972, 1973 and 1974. This data is further illustrated in Figures 1a–d. Figure 1a shows the distribution of the number of deliveries per year. Figure 1b shows the distribution of the total number of cesarean sections per

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From the Department of Obstetrics and Gynecology of Mount Sinai School of Medicine of The City University of New York; The City Hospital Center at Elmhurst; and The Mount Sinai Hospital, New York, N.Y. 10029.

Requests for reprints should be sent to: Dr. R. Nachamie, Department of Obstetrics and Gynecology, The Mount Sinai Hospital, Fifth Avenue and 100 Street, New York, N.Y. 10029.

TABLE IA

Distribution of Cesarean Sections City Hospital Center at Elmhurst 1971–1974

Patients number

Year	Deliveries	Cesarean sections	% of total C/S
1970	2075	129	6.2
1971	1801	138	7.7
1972	1848	185	10.0
1973	1881	146	7.8
1974	1514	141	9.3

TABLE IB

Distribution of Cesarean Sections City Hospital Center at Elmhurst 1971–1974

Year	Patients number (percent)			
	Total 1°C/S	Primip 1°C/S	Multip 1° C/S	Total repeat C/S
1970	70 (3.4)			59
1971	88 (4.9)	55	33	50
1972	120 (6.5)	79	41	65
1973	87 (4.6)	62	25	59
1974	97 (6.4)	61	36	44
Total		257	135	

year. Figure 1c shows the number of primary cesarean sections per year. Figure 1d shows the distribution of primary cesarean sections in primiparous and multiparous patients and their relationship to each other.

We see that there is a slight rise in the numbers in 1972 with a subsequent apparent decline in 1973 and 1974. This, however, is probably not a true decline, since it was during the latter two years that all "high risk" patients and any scheduled cesarean sections were diverted from the City Hospital Center due to partial closure of the labor, delivery, and cesarean section suites for construction and repairs at the City Hospital.

Table II affords a comparison of the Elmhurst statistics with those from the 1974 annual report from the Department of Obstetrics at The Mount Sinai Hospital. The number of cesarean sections performed on the private service was 246, or 14.7% of all deliveries and the number of cesarean sections performed on the ward service was 236 or 16.1%. We do not have the data to separate these figures into primary cesarean sections performed on primiparous versus multiparous patients but we do note an absolute difference in the percentage of total cesarean sections.

Table III lists maternal and fetal factors of the population studied. Among the primiparous patients having undergone primary cesarean sections, the ages range from 15 years to 43 years. The mode was 22 with 20 years of age second in frequency. The average age was 28.1. The age range of the multiparous patients was from 17 years to 42. The mode was 29 with 34 years of age second in frequency. The average age was 29.04 years. This data is further illustrated in Figures 2a and 2b.

The racial backgrounds were varied, with the Spanish population predominating and the blacks second in frequency. (Fig. 3). These races have been

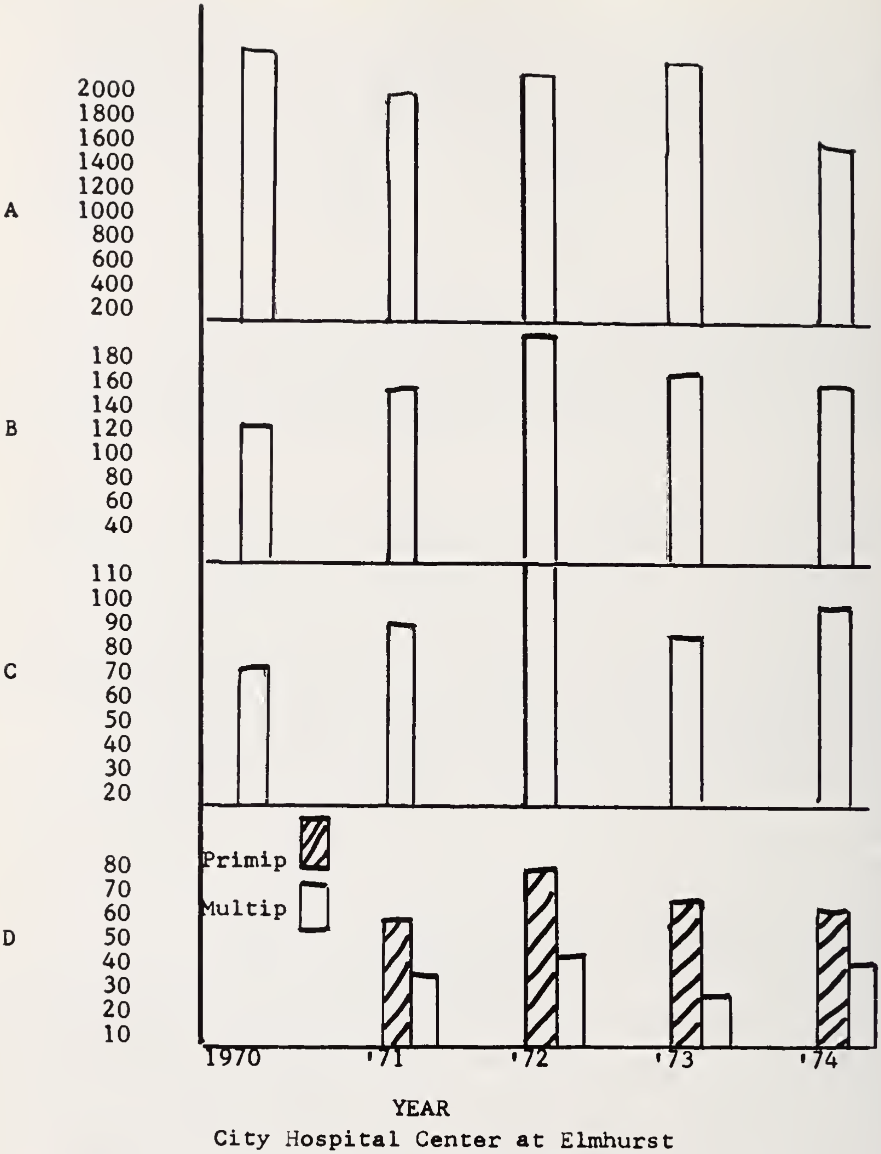

Fig. 1. Distribution per year of a. number of deliveries; b. total number of cesarean sections; c. number of primary cesarean sections; d. relationship of primary cesarean sections; in primiparous and multiparous patients.

TABLE II

Cesarean Sections Mount Sinai Hospital 1974

	Patients number (percent)		
	Private	Ward	Total
Cesarean Sections	246 (14.7)	236 (16.1)	482 (15.3)

TABLE III

Maternal and Fetal Data

		Primip.	Multip.
maternal age	aver.	28.1	29.04
	range	15–43	17–42
	mode	22 (20)	29 (34)
maternal race	Spanish	182	112
	Black	32	13
	Mid East	14	2
	Far East	8	3
	Caucasian	18	5
	Haitian	5	—
parity	aver.		5.78
	range		1–11
	mode		(1)
birthweight (pounds)	aver.	7.2	7.1
	range	2–14	3–12
	mode	8	8
previous birthweight	aver.		7
	range		5–9
	mode		7

described as having less favorable pelves for vaginal delivery and some are of smaller stature than the average caucasian female of the New York Metropolitan area.

The parity ranged from 1 to 11 with a mode of 1 and a median of 5.78. (Fig. 4).

The weights of the newborns ranged from 2 to 14 pounds in the primary cesarean sections of the primiparous patients and 3 to 12 pounds in the multiparous patients. The mode in both was 8 pounds and the median was 7.2 pounds in the primiparas and 7.1 pounds in the multiparas.

The weights of the previous births of the multiparous patients ranged from 5 to 9 pounds with a mode and median of 7 pounds.

Indications for Primary Cesarean Section

Table IV lists the indications for primary cesarean sections in the primiparous and multiparous patients. The leading cause was pelvic contraction and mechanical dystocia. Breech pelvic disproportion, in more recent years, is playing an increasing role as an indication for primary cesarean section in the multiparous patient. This should provide a healthier outcome for mother and baby. The reasons for this have been well cited in the work of Rovinsky, Miller, and Kaplan (9). Cephalo-pelvic disproportion is an insidious cause of dystocia in the multipara and must be kept in mind to avoid unnecessary delay in primary abdominal delivery of the multiparous patient. This represents 117 or 45.5% of the total primary cesarean sections performed in primiparas and 27 or 20% of primary cesarean sections performed on multiparas.

The other indications for cesarean section as listed in Table IV are: pre-

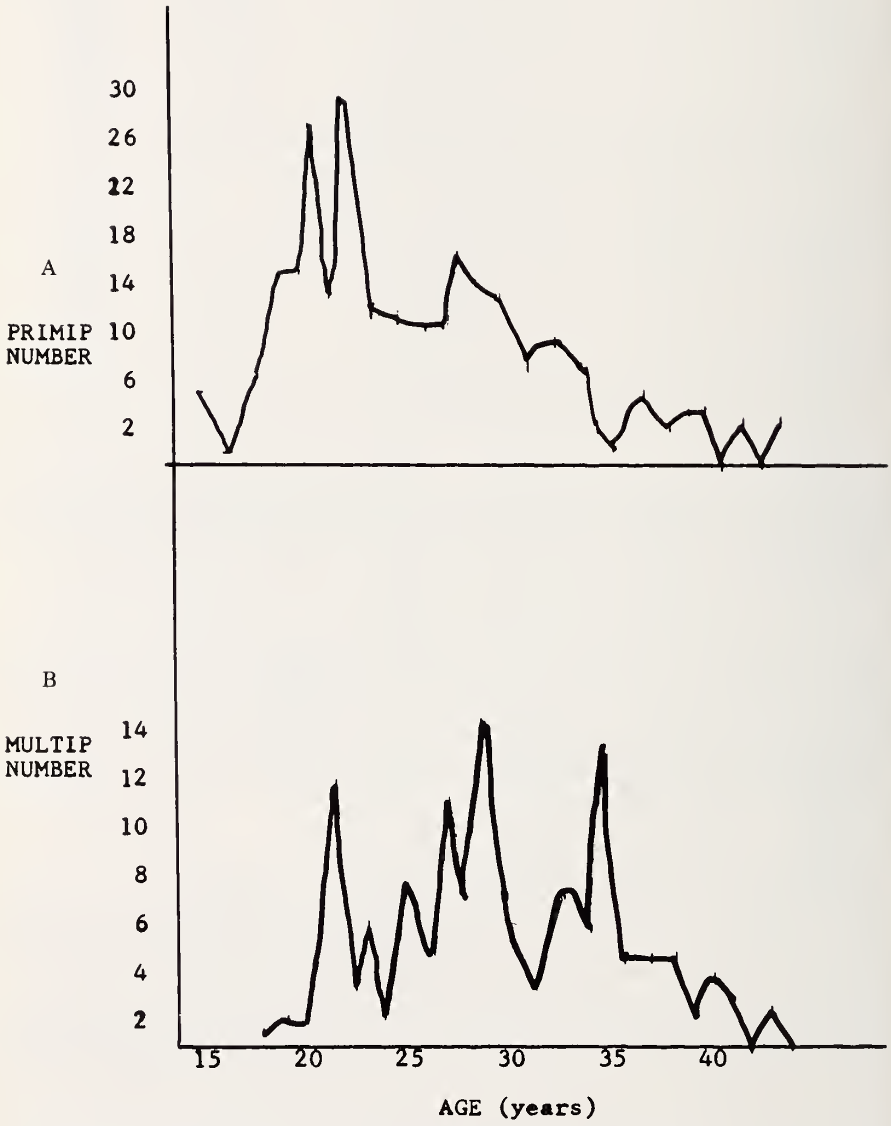

Fig. 2. Age distribution of 1° C/S in patients at the CHCE 1971–1974; a. Primp; b. Multip.

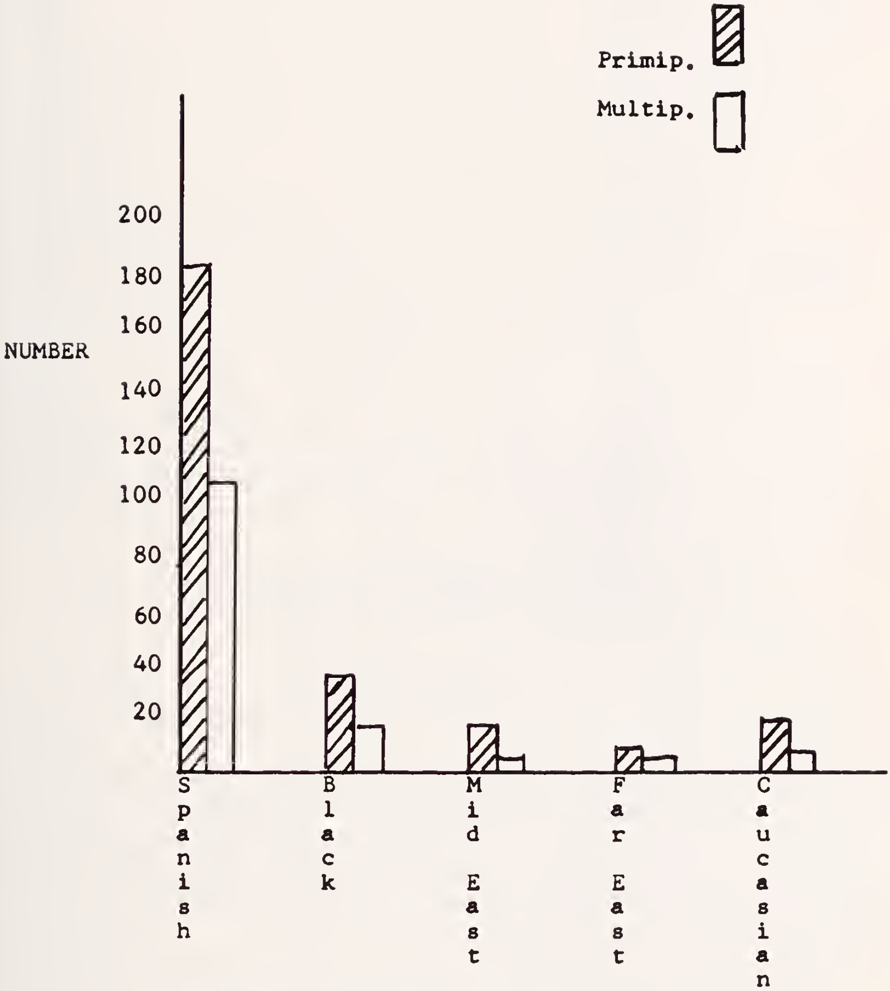

Fig. 3. Racial distribution of 1° C/S Primips. and Multips.

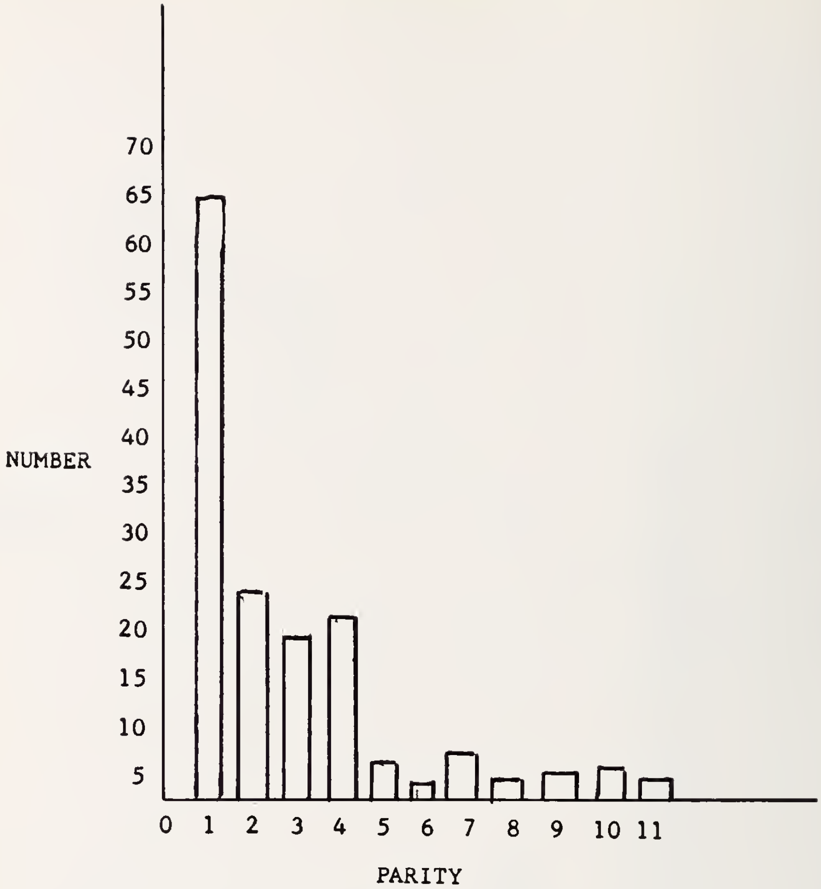

Fig. 4. Parity distribution of primary C/S in multiparous patients from 1971–1974.

vious surgery, hemorrhage, toxemia, diabetes, cord prolapse, fetal distress, failure of progress in labor (uterine inertia) and amnionitis.

Table V lists the indications for all primary cesarean sections at the Mount Sinai Hospital in 1974. Pelvic contraction and mechanical dystocia represent 60.5% of the total. This number is similar to that previously listed at the City Hospital Center at Elmhurst.

The series of primary cesarean sections at the City Hospital Center at Elmhurst had 4 fetal deaths. Two were secondary to congenital malformations incompatible with life. One was secondary to prematurity following an emergency cesarean section for placental abruption, where the fetus weighed two pounds. One primigravida and her fetus died following a cesarean section, at 28 weeks, for toxemia superimposed on severe chronic hypertension (Table VI).

Concomitant Surgical Procedures

(Tables VII and VIII)

At the City Hospital Center at Elmhurst there were 20, or 14.8%, bilateral tubal ligations performed along with the primary cesarean sections in multi-

TABLE IV

Indications for primary C/S City Hospital Center Elmhurst 1971–1974

Indication	Patients: number (percent)	
	Primip.	Multip.
pelvic contraction/mechanical dystocia	169 (65.8)	68 (50.4)
a—cpd	117 (45.5)	27 (20)
b—bpd	45 (17.5)	27 (20)
c—fibroid blocking	1	0
d—trans	5	10
e—mentum post	0	2
f—face	1	1
g—compound	1	0
h—locked twins	0	1
previous surgery		
a—myomectomy, hysterotomy	6 (2.3)	2
b—colporrhaphy	0	3
hemorrhage	12 (4.7)	12 (8.9)
a—abruption	7	4
b—previa	5	8
toxemia	21	10
diabetes	6 (2.3)	7 (5.2)
cord prolapse	7	8
fetal distress (90% with monitor)	34 (13.2)	24 (17.8)
failure to progress (secondary uterine inertia)	24 (9.3)	21 (15.6)
amnionitis	11	1

TABLE V

Indications for primary C/S Mount Sinai Hospital 1974

	Patients: number (percent)		
	Private	Ward	Total
pelvic contraction/mechanical dystocia	95 (62.0)	86 (58.1)	181 (60.5)
a—cpd	91	82	173
b—bpd	1	1	2
c—trans	2	0	2
previous surgery	4 (2.6)	5 (3.4)	9 (3.0)
Hemorrhage	3 (2.0)	12 (8.1)	15 (5.0)
toxemia	3 (2.0)	8 (5.4)	11 (3.7)
diabetes	10 (6.6)	9 (6.1)	19 (6.4)
prolapse of cord	1 (0.7)	4 (2.7)	5 (1.7)
fetal distress	16 (10.6)	13 (8.8)	29 (9.7)

TABLE VI

Fetal and Maternal Deaths

Total Deaths: 4 fetal
1 maternal

1—primiparous patient, age 28 with essential hypertension and superimposed toxemia, delivered at 28 weeks, mother and infant died within several days of the operation.

1—multiparous patient, 1° C/S for placental abruption, premature infant, birthweight 2 pounds, died shortly after birth.

1—multiparous
and
1—primiparous } patient delivered infants with multiple congenital anomalies incompatible with sustained life

TABLE VII

Primary Cesarean Sections and Concomitant Surgery City Hospital Center Elmhurst 1971–1974

	Primip.	Multip.
Bilateral tubal ligation	0	20 (14.8%)
hysterectomy		
a – fibroids	1	7
b – C.I.N.	0	1
Myomectomy	1	0
unilateral salpingo-oophorectomy	1	0
Type of uterine incision:		
low flap transverse	256	121
low flap vertical	0	4
classic	0	3
classic with cesarean hysterectomy	1	7

TABLE VIII

Primary Cesarean Sections and Concomitant Surgery, Mount Sinai Hospital 1974

	Patients: number (percent)		
	Private	Ward	Total
low segment uterine incision	150 (99.3)	116 (78.4)	266 (89.0)
low segment uterine incision and sterilization	1 (0.7)	26 (17.6)	27 (9.0)
classic uterine incision	0	1 (0.7)	1 (0.3)
classic uterine incision and sterilization	0	3 (2.0)	3 (1.0)
Cesarean hysterectomy indicated	0	1 (0.7)	1 (0.3)
cesarean hysterectomy sterilization	0	1 (0.7)	1 (0.3)
Total	151 (100)	148 (100)	299 (100)

paras and one cesarean hysterectomy for cervical intraepithelial neoplasia (CIN) (Table VII). Four of the low flap cesarean sections in the multiparas were vertical low flap incisions (to avoid varicosities and a marginal placenta previa outlined by diagnostic ultrasound).

There were 7 cesarean hysterectomies performed on the multiparas for fibromyomata uteri. The 7 cesarean hysterectomies had classic uterine incisions for delivery of the baby and three additional classic cesarean sections were performed upon multiparous patients who had placenta previas.

Among the primiparous patients undergoing primary cesarean sections there was one cesarean hysterectomy performed on a patient who had a multinodular fibroid uterus. One other primiparous patient had a right salpingo-oophorectomy performed with a cesarean section and another had a single myomectomy performed along with the primary cesarean section. Two hundred and fixty-six of the 257 cesarean sections performed on the primiparous patients were low flap transverse cesarean sections. The one cesarean hysterectomy had a classic incision for delivery of the baby.

Table VIII lists the cesarean sections and concomitant surgery performed at The Mount Sinai Hospital in 1974. There was 1 classic cesarean section or 0.3% and there were 2 cesarean hysterectomies.

Discussion

This review is made in order to reinforce some of the factors necessitating a primary cesarean section in the primiparous and multiparous patient. The intent is to further decrease fetal and maternal morbidity as listed in Table IX.

Conclusion

Careful surveillance for the indications for primary cesarean section in the multiparous patient should continue. This is facilitated by the increasingly extensive use of, and skill with, the following modalities:

1. fetal monitoring
2. diagnostic ultrasound (to aid in estimation of fetal size, placental location, genetic amniocentesis)
3. amniocentesis and analysis of the fluid thus obtained.

Maternal and fetal outcome of cesarean section is further improved by the

TABLE IX

Maternal and Fetal Morbidity and Mortality

Maternal Trauma
1 – rectal sphincter damage
    recognized and unrecognized
2 – bladder injury
    recognized and unrecognized
3 – sulcus tears
4 – cervical lacerations with and without lower uterine segment extension
5 – uterine rupture
    spontaneous or following; version, difficult forceps delivery, difficult breech extraction, pitocin stimulation, fundal pressure
6 – hemorrhage
    immediate
    late

Fetal Trauma – exacerbated with; breech delivery and after coming head, cephalo-pelvic disproportion, shoulder dystocia
1 – orthopedic and neurologic
    fracture
    dislocation
    paralysis
    paresis
2 – cerebral
    tentorial tears
    hematoma
    fracture
3 – truncal damage
    liver, kidney, or spleen injury
4 – pulmonary, aspiration
    blood, meconium, amniotic fluid

constant availability on the labor floor of experts in obstetrical anesthesia and neonatology.

A low cesarean section rate is not necessarily a thing of which to be proud. We must strive to perform no more or less than necessary. Fortunately, the grand multipara with her added risks is, in our population, almost a thing of the past. The multiparous patient should be afforded the same consideration as her primiparous counterpart. Avoidance of prolonged labor and traumatic delivery will be of aid to the mother, child and obstetrician. We repeat what others have said, avoid the false sense of security when caring for the pregnancy, labor, and delivery of a multiparous patient.

References

1. Hospital-Mount Sinai School of Medicine: Annual Report, Department of Obstetrics, January 1974–December 1974.
2. Dill, L. V., et al: Cesarean Section for Disproportion in the Multipara, Amer J Obstet Gynec 56:515, 1948.
3. Duckman, S., et al: Disproportion in Multipara Fact or Philosophy, Amer J Obstet Gynec 101:1001, 1968.
4. Eastman, N. J.: The Hazards of Pregnancy and Labor in the "Grande Multipara," NY State J Med 1708, 1940.
5. Klein, M. D., Robbins, R., and Gabaeff, L.: Primary Cesarean Section in the Multipara, Amer J Obstet Gynec 87:242, 1963.
6. Miller, E.: Grand Multiparas, Obstet Gynec 4:418, 1954.
7. Nelson, J. H., and Sandmeyer, M. W.: A Study of 812 Grand Multiparas, Amer J Obstet Gynec 75:1262, 1958.
8. Oxorn, H.: Hazards of Grand Multiparity, Obstet Gynec 5:150, 1955.
9. Rovinsky, J. J., Miller, J. A., and Kap, S.: Management of Breech Presentation at Term, Amer J Obstet Gynec 115:497–513, 1973.
10. Sambhi, J. S.: Obstetric Problems Created by Increasing Fetal Size in Developing Communities, J Gynaec Obstet 11:51, 1973.
11. Schram, E. L. R.: The Problem of the Grand Multipara, Amer J Obstet Gynec 67:253, 1954.
12. Sogolow, S. R. and Friedman, E. A.: Fetopelvic Disproportion in Multipara, Obstet Gynec 29:848, 1967.
13. Tancer. M. L. and Vandenberg, W.: Disproportion in the Multipara, Obstet Gynec 14:753, 1959.
14. Van Praagh, I. G. and Tovell, H. M. M.: Primary Cesarean Section in the Multipara, Obstet Gynec 32:813–825, 1968.

The Mount Sinai Journal of Medicine
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

Intramedullary Serotonin Patterns following Experimental Spinal Cord Trauma

ROBERT A. BRODNER, M.D., GEORGE J. DOHRMANN, M.D., Ph.D., and
ROBERT H. ROTH, Ph.D.

Recent studies of spinal cord trauma suggest that the contused spinal cord is affected not only by direct mechanical injury at the time of impact, but that after trauma, there occur secondary pathophysiologic responses of the spinal cord and its blood supply which may cause further damage (1). Among the various pathologic processes occurring in the traumatized spinal cord are changes in monoamine metabolism (2–9). An alteration of serotonin in neural tissue after experimental trauma has been reported by several investigators (7, 9). However, the concentration of spinal cord serotonin at various time intervals after injury has not been closely studied. A definition of the pattern and temporal distribution of intramedullary serotonin following spinal cord contusion may have importance relative to the concomitant vascular alterations which occur posttrauma (10–12).

Controversy surrounds the role of intramedullary serotonin following spinal cord injury. Indeed, if serotonin is involved in secondary damage attendant on significant trauma, the clinical and therapeutic implications of a potentially reversible pathobiochemical substrate are clear. The purpose of the present study is to define intramedullary serotonin patterns during the first 12 hours following experimental contusion of the cat spinal cord using a standardized trauma model previously established in this laboratory (13–15).

Materials and Methods

Cats weighing 2 to 4 kilograms were pretreated 24 hours prior to the experiment with iproniazid (100 mg/Kg), a monoamine oxidase inhibitor.*

From the Department of Neurosurgery, Mount Sinai School of Medicine of The City University of New York; and Section of Neurosurgery, Department of Surgery and Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut.

Presented in part at the European Congress of Neurosurgery, Oxford, England, September 15, 1975.

Supported by Grant NS 10174 from the National Institute of Neurological and Communicative Disorders and Stroke.

Requests for reprints should be sent to: Robert A. Brodner, M.D., Department of Neurosurgery, Mount Sinai School of Medicine of The City University of New York, Fifth Avenue and 100 Street, N. Y. 10029.

* Previous pilot data from our laboratory has demonstrated that to most accurately determined subtle patterns of change in serotonin concentration within the traumatized spinal cord, pretreatment with a monoamine oxidase inhibitor, such as iproniazid, is indicated. Iproniazid is completely cleared from the animal within 24 hours, although monoamine oxidase is totally inactivated for approximately 2 weeks while resynthesis occurs (17). Therefore, any nonspecific side effects of this agent were removed by the time of the experiment.

Tracheostomy was performed following anesthesia with intraperitoneal pentobarbitol (35 mg/Kg). Muscular paralysis was achieved with the intravenous administration of gallamine triethiodide. Respirations were controlled with a Harvard small animal respirator. The end-expiratory pCO_2 was monitored with a Beckman gas analyzer and maintained between 2 to 4%. Catheters were placed into the femoral vein for fluid replacement and the administration of drugs, and into the femoral artery for continuous blood pressure monitoring. The rectal temperature was maintained between 36° and 38°C by external heat sources. Screw electrodes were placed into the skull over the right and left primary somatosensory areas. Stimulating electrodes were positioned over the contralateral posterior tibial nerve and a 0.1 msec pulse of 1 V/sec was used. The cortical transients were channelled to a Biomac 1000 computer for analysis. Cortical evoked responses were recorded before trauma, immediately after trauma, and just prior to the sacrifice of each animal. A laminectomy was performed from C_2 through C_4 and the spinal cord was traumatized using a modification (16) of the weight-dropping technique described by Allen (18) and Albin et al (19). A 20 gm weight was allowed to fall 25 cm through a vertically oriented tube to strike an impounder resting on the spinal cord, thereby delivering a contusion force of 500 gm-cm.

Eighteen animals were divided into groups of three and studied at the following time intervals: 5 min, 15 min, 30 min, 1 hr, 4 hrs and 12 hrs after trauma. Four nontraumatized cats, studied at 5 min or 1 hr postlaminectomy, served as controls. At one of the specified time intervals following contusion, the exposed portion of spinal cord was excised and assayed for serotonin. Total 5-hydroxyindoles were determined by a modification of the orthophthaldialdehyde condensation method of Atack and Lindqvist (20). Spinal cord tissue blanks and internal standards were run for each sample. Total 5-hydroxyindoles were equated with serotonin as monoamine oxidase was inhibited. A serotonin standard was used, and the product expressed as nanograms (ng) of serotonin per gram of tissue.

Results

The results of the spinal cord serotonin assay are shown in Table I. When compared to the control group no statistically significant elevation in the serotonin content of the traumatized spinal cord was noted during the 12 hours studied. At 30 minutes post-trauma the serotonin concentration was low (442 ng/gm), and was significantly ($p < 0.05$) less than that of the 1 hour postlaminectomy controls. In all animals, the cortical evoked response was absent immediately following 500 gm-cm spinal cord impact, and did not return during the period monitored.

Discussion

Altered serotonin metabolism has been associated with various pathophysiological events and related neurologic findings (7, 9, 21–24). Increased free serotonin in neural tissue depresses the reticular formation, the cardiorespi-

TABLE I

*Concentration of Spinal Cord Serotonin**

Group	Time	Serotonin (ng/gm)
Control	Postlaminectomy	
	5 min	626 ± 76
	1 hr	742 ± 112
Trauma	After Injury	
	5 min	679 ± 160
	15 min	683 ± 65
	30 min	442 ± 48**
	1 hr	678 ± 49
	4 hr	664 ± 73
	12 hrs	708 ± 78

* Values given as means ± the standard error of the mean.

** Significantly lower when compared to the 1 hr control group at $p = <0.05$.

ratory centers and general neuronal activity (7, 24). Welch et al (24) noted increased free serotonin in brain tissue concomitant with cerebral ischemia in baboons, and suggested that serotonin plays a significant role in the pathogenesis of the symptoms and signs which accompany cerebral infarction. Berzin et al (22) have implied that damage to the blood-brain barrier caused by ischemia/hypoxia might enhance movement of free plasma serotonin into the brain and cerebrospinal fluid of patients with acute ischemic cerebrovascular disease. Elevated levels of serotonin in the brain may be responsible for progressive brain infarction and impairment of collateral circulation secondary to the vasoconstrictor effect of serotonin on the cerebral microvasculature (21, 24).

Recent studies have suggested a role for serotonin in traumatic neurological conditions. Alterations in serotonin levels in neural tissue have been measured in animals following injury. Osterholm and Meyer (7) have reported elevated levels of serotonin in the brain and CSF after experimental cerebral trauma in cats. The authors (7) hypothesized that, when released from an intracellular site, serotonin acts on other neurons to cause post-traumatic neurologic deficits. Zivin et al (9) have noted substantial changes in monoamine concentrations following spinal cord trauma with an increase in serotonin within the white matter 2.5 times that of controls. Osterholm et al (7) have shown that minute quantities of serotonin injected intracerebrally cause severe neurologic alterations and cerebral edema. Other investigators, however, have been unable to confirm either a direct neurotrophic effect of serotonin or an increase in serotonin in the central nervous system after trauma (4, 25).

The results of this study are in agreement with the reports of Naftchi et al (6) and de la Torre et al (4) who studied serotonin concentrations at 1 hour after experimental spinal cord injury, and observed no elevation. In addition, we have studied the intramedullary serotonin pattern through 12 hours post-trauma and have noted a significant ($p < 0.05$) decrease in the serotonin concentration 30 minutes following injury.

Studies of the blood flow patterns in the intramedullary microcirculation following spinal cord injury have demonstrated a transient vasoconstriction and decreased perfusion in the microvasculature of the white matter within the first hour after trauma (10–12). These changes are characterized by a biphasic blood flow pattern in the traumatized tissue as manifested by reduced perfusion at 15 minutes and 1 hour following injury with improved circulation at 30 minutes as well as 4 and 12 hours post-trauma (10–12). The relative anoxia produced by decreased intramedullary perfusion at the 15 minute post-trauma interval, may depress serotonin synthesis which is oxygen dependent (26). The low serotonin content of the spinal cord at 30 minutes after injury may be a reflection of this diminished synthesis. As more adequate perfusion and oxygen availability occur, synthesis may increase and the serotonin concentration becomes higher, as indicated by the serotonin levels at 1 hour post-trauma (Table I).

This study demonstrates no statistically significant increase in spinal cord serotonin after experimental trauma; and, therefore, does not confirm the work of other investigators (7, 9) who reported elevated tissue serotonin following central nervous system contusion. Indeed, we have shown a significant decrease in spinal cord serotonin levels 30 minutes after injury, which is most likely due to altered intramedullary microcirculatory dynamics and resultant transient depression of serotonin synthesis.

Preliminary data from our laboratory demonstrates significant alterations in cerebrospinal fluid serotonin concentration following spinal cord injury (27, 28). The nature of these changes and their correlation with blood flow patterns in the contused spinal cord are currently being studied.

References

1. Osterholm, J. L.: The Pathophysiological Response to Spinal Cord Injury. The Current Status of Related Research, J Neurosurg 40:3, 1974.
2. Brodner, R. A. and Dohrmann, G. J.: Norepinephrine, Dopamine and Serotonin in Experimental Spinal Cord Trauma, Current Status, Paraplegia (In Press).
3. Brodner, R. A. and Dohrmann, G. J.: Norepinephrine, Dopamine and Serotonin in Experimental Spinal Cord Trauma. Presented at the Annual Scientific Meeting of the International Medical Society of Paraplegia, Toronto, August 5, 1976.
4. de la Torre, J. C., Johnson, G. M., Harris, L. H., Kajihara, K., and Mullan, S.: Monoamine Changes in Experimental Head and Spinal Cord Trauma: Failure to Confirm Previous Observations, Surg Neurol 2:5, 1974.
5. Hedeman, L. S., Schellenberger, M. K., and Gordon, J. H.: Studies in Experimental Spinal Cord Trauma. Part 1: Alterations in Catecholamine Levels, J Neurosurg 40:37, 1974.
6. Naftchi, N. E., Demeny, M., Kertess, A., and Lowman, E. W.: The CNS and Adrenal Tyrosine Hydroxylase Activity and Norepinephrine, Serotonin and Histamine in the Spinal Cord after Transsection, Fed Proc 31:3484, 1972.
7. Osterholm, J. L., Bell, J., Meyer, R., and Pyenson, J.: Experimental Effects of Free Serotonin on Brain and Its Relation to Brain Injury, J Neurosurg 31:408, 1969.
8. Rawe, S. E., Roth, R. H., D'Angelo, C. M., Biber, M. C., and Collins, W. F.: Norepinephrine Levels in Experimental Spinal Cord Trauma. Presented at American Association of Neurological Surgeons, Saint Louis, April 22, 1974.
9. Zivin, J. A., Doppman, J. L., Reid, J. J., Tappaz, M. L., Saavedra, J. M., Kopin, I. J., and Jacobowitz, D. M.: Biochemical and Histochemical Studies of Biogenic Amines in Spinal Cord Trauma, Pharmacologist 17:264, 1975.
10. Allen, W. E., D'Angelo, C. M., and Kier, E. L.: Correlation of Microangiographic and

Electrophysiologic Changes in Experimental Spinal Cord Trauma, Radiol 111:107, 1974.

11. Brodner, R. A., and Dohrmann, G. J.: Intramedullary Blood Flow Patterns within the Upper Cervical Spinal Cord following Experimental Traumatic Paraplegia (Unpublished).
12. Dohrmann, G. J. and Allen, W. E.: Microcirculation of Traumatized Spinal Cord: A Correlation of Microangiography and Blood Flow Patterns in Transitory and Permanent Paraplegia, J Trauma 15:1003, 1975.
13. Brodner, R. A., VanGilder, J. C., and Collins, W. F.: The Effect of Anti-fibrinolytic Therapy in Experimental Spinal Cord Trauma, J Trauma 17:48, 1977.
14. Brodner, R. A., VanGilder, J. C. and Collins, W. F.: Experimental Spinal Cord Trauma: The Efficacy of Treatment. Presented at the American Association of Neurological Surgeons, San Francisco, April 5, 1976.
15. Taub, A., Collins, W. F., Hamill, B., D'Angelo, C. M., Wagner, F. C., and Dohrmann, G. J.: Trauma Dose-Response Relationships for Standardized Spinal Cord Trauma in Cats. Presented at American Association of Neurological Surgeons, Miami, April 8, 1975.
16. Dohrmann, G. J., Panjabi, M. M., andWagner, F. C., Jr.: An Apparatus for Quantitating Experimental Spinal Cord Trauma, Surg Neurol 5:315, 1976.
17. Goodman, L. S. and Gilman, A. *The Pharmacological Basis of Therapeutics*. The Macmillan Company, 1704 pp., 1975.
18. Allen, A. R.: Surgery of Experimental Lesion of Spinal Cord Equivalent to Crush Injury of Fracture Dislocation of Spinal Column, JAMA 57:878, 1911.
19. Albin, M. S., White, R. J., Acosta-Rua, G., and Yashon, D.: Study of Functional Recovery Produced by Delayed Localized Cooling after Spinal Cord Injury in Primates, J Neurosurg 29:113, 1968.
20. Atack, C. and Lindqvist, M.: Conjoined Native and Orthophthaldialdehyde Condensate Assays for the Fluorometric Determination of 5-hydroxyindoles in Brain, Naunyn Schmiedebergs Arch Pharmacol 279:267, 1973.
21. Bell, W. H., Sundt, T. M., and Nofzinger, J. D.: The Response of Cortical Vessels to Serotonin in Experimental Cerebral Infarction, J Neurosurg 26:203, 1967.
22. Berzin, Y. E., Auna, Z. P., and Brezhinsky, G. Y.: The Significance of Blood Serotonin and CSF in the Clinical Picture and Pathogenesis of Acute Cerebral Circulatory Disturbance, Zh Neuropat Psikhiat 69:1011, 1969.
23. Danis, R. K., and Willman, V. L.: Cerebral Air Embolism Effects on Brain Water and Serotonin Content, Surg Forum 14:63, 1963.
24. Welch, K. M. A., Meyer, J. S., Teraura, T., Hashik, and Shinmaru, S.: Ischemic Anoxia and Cerebral Serotonin Levels, J Neurol Sci 16:85, 1972.
25. Naftchi, N. E., Demeny, M., De Crescito, V., Tomasula, J. J., Flamm, E. S., and Campbell, J. B.: Biogenic Amine Concentrations in Traumatized Spinal Cords of Cats. Effect of Drug Therapy, J Neurosurg 40:52, 1974.
26. Hagen, P. B. and Cohen, L. H.: Biosynthesis of Indolealkylamines. Physiological Release and Transport of 5-hydroxytryptamine. In *Handbook of Experimental Pharmacology*, Edited by O. Eichler and A. Farah. Vol. 19, p. 184. Springer-Verlag, Berlin 1966.
27. Brodner, R. A., Dohrmann, G. J., and Roth, R. H.: Elevation of 5-hydroxytryptamine in the Cerebrospinal Fluid following Experimental Spinal Cord Injury, Brain Research 118:348, 1976.
28. Brodner, R. A. and Roth, R. H.: The effect of Parachlorophenylalanine and Reserpine in Experimental Spinal Cord Trauma. Part 1: Altered 5-hydroxytryptamine Levels in the Spinal Cord and Cerebrospinal Fluid (Unpublished).

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

New Approaches to Patient Care in the Hospital Setting

SIDNEY LEIBOWITZ, M.D.

Abstract

Many factors are compelling us to reexamine our methods of teaching and delivering health care: financial, personnel, social, educational. For these, and other reasons, interest has increased in the general problem of primary medicine by whatever name it is known. Additional impetus to incorporating the teaching of ambulatory care in the training of the internist has been given by the policy statement of September 11, 1974 of the American Board of Internal Medicine. Commitment by departments of Medicine are vital for the success for such programs. At Beth Israel Medical Center in New York such a commitment exists. It has led to a carefully derived and supervised program to teach ambulatory health care to residents in Medicine. It is predicated on identification of the resident as the patient's primary physician with responsibility for continuing comprehensive care for that patient during his entire residency training period.

Introduction to the General Problem of Primary Medicine: Concepts and Traditions

Both by written and spoken word we are being bombarded steadily these days by a barrage on the general subjects of the "first-contact physician" and the "complete internist," which undoubtedly leaves most of us wondering, confused, and perhaps alienated. "Bewildering babel" is one observer's characterization of this (1), but this attitude appears to ignore the many thoughtful, scholarly, and provocative essays on the subject (2–10). Yet, like corks on turbulent waters, certain terms repeatedly surface—"Primary Medicine" (not to mention secondary and tertiary), "Primary Physician," "Family Medicine," "Family Doctor," "General Practice"—with no accompanying illuminating or precise definitions. Recognized bodies who speak for Internal Medicine specialists, such as the American College of Physicians and the American Board of Internal Medicine, have long engaged in a search for the precise definition of an internist. The many suggestions they propose point up the absence yet of a satisfactory single answer.

To this broad subject of "Primary Medicine" (the term I shall use for the moment for want of a better term) must be added the widening acceptance of the need for increased exposure of our medical students and house officers to ambulatory patient care, as opposed to the almost total reliance heretofore on in-hospital patient care for such teaching.

From the Departments of Medicine and of Ambulatory Health Services, Beth Israel Medical Center, New York N.Y.; and Mount Sinai School of Medicine of The City University of New York, N.Y.This paper was originally read on October, 1975 at the meeting of the Medical Alumni Association of the University of Rochester School of Medicine and Dentistry, Rochester, New York.

Requests for reprints should be sent to: Sidney Leibowitz, M.D., 325 East 16 Street, New York, N.Y. 10003.

Traditionally we are taught and trained in medicine on the sick person, the sicker the better for such learning purposes, and this inevitably leads us for such learning to the bedded-down patient. The approach to teaching is by diseases and by thorough understanding of the pathophysiology of each such disease state, be it infectious or degenerative or inflammatory by virtue of still not understood etiologies. (Systemic lupus erythematosus comes to mind as a prime illustration.) Such learning is predicated on the ultimate in seriousness of illness and outcome. Hence, the stress was placed upon pathology and tissue studies.

I would not change this concentration on the understanding of disturbed bodily functioning while studying its morphologic effects upon tissues and organs. But even in my student days, still in advance of the forthcoming general acknowledgment and recognition of the importance of the psychosomatic and psychiatric factors in medicine, we were exposed to outpatients to some degree. Usually this was in Medicine in our fourth year; and perhaps electively as on Saturdays in the L (Luetic) clinic; or as an extraordinary exposure (as in my case) to ENT as a substitute for an intern who was ill.

In the past the graduate as house officer was exposed almost exclusively to inpatients in that precious, ensuing learning period as he ascended the ladder from intern to resident. Rounds at the bedside were the height of this educational period. Conferences and Grand Rounds were punctuated effectively by the rolling in of the bedded patient to the amphitheater or auditorium, during or after the clinical presentation. On rare occasion, the patient under discussion would be invited back ambulatorily to demonstrate clinical features or underscore the effectiveness of therapy, but to the students and house staff, therapy was generally subordinated to the sharpening of clinical skills in diagnosis and understanding of the disease process. The patient as a vibrant, individual person, as a family member, as a wage earner or nonearner, parent or sibling, of this or that occupation, society contributor or not, integrated community member were factors rarely a subject for discussion.

Factors Provoking a Rethinking in Health Care Delivery

Be that as it may, the pressure is now upon us additionally to approach problems of patients and general health care from another direction; namely, in an ambulatory or come-and-go status, for patients who are sleeping at home at night, with a planned comprehensive approach utilizing other health professionals. The reasons are many for interest in this altered pathway for delivery of health care.

Financial

In-hospital care is too expensive to support at its current rate of acceleration. Reasons for this include, among others, the total national bill for delivery of health care; the increasing interest of government and third-party payers and the public (the "consumer") in this area of cost; the extraordinary expense of manpower training, research and the exquisite and sophisticated machinery and equipment of modern scientific breakthroughs; the spiraling costs of hospital construction; the over-construction of the 1960's and the understandable threat to institutional survival if bed occupancy is not maintained at high levels despite the recognition that, from the standpoint of strict medical need, many such beds are actually over-occupied.

Personnel

A polemic continues about the sufficiency of physicians for the health care needs of the country. I will not attempt to delineate the problems or adjudicate the various contentions, but for our purpose here it should be conceded that certain segments of our population do receive less satisfactory care than others. For the less privileged, there is an insufficiency of medical manpower, even if due to the generally acknowledged maldistribution of doctors, rather than to a not so generally acknoweldged insufficient total numbers.

Whether or not anticipated National Health Insurance (added to the Medicare and Medicaid advances since 1966) will solve this need, there is no doubt that more effective use and perhaps redistribution of our medical pool are in order. The day is now at hand for an attempt at intelligent utilization of physician extenders. I do not exclude our nurse colleagues from this role.

Social

It is futile to contest the repeated claim of lay people that, away from his office or the hospital, the physician is less and less available to the patient. This is true. I do not know how practice is conducted in Rochester these days, but for a long time I was reluctant to concede this point with respect to my community in New York City where I have practiced for many years. But I am a late believer. For this and other socially derived reasons, the slack that developed has had to be picked up by Emergency Rooms throughout the country, so that the nature of Emergency Services is greatly changed. Thus has resulted, de novo, an extraordinary ambulatory service.

Educational

There have been appraisal and reappraisal by the supervisory bodies in Internal Medicine (not to mention the other disciplines doing the same). The soundness of the training and certification process in Internal Medicine has again been questioned in recent years and the clock has been turned back. Finally, on September 11, 1974, the American Board of Internal Medicine has, in effect, pleaded for return toward mixed type house staff training in preparing the internist for his Boards, with a view to "certify[ing] internists capable of rendering excellent primary care" (11). This return to rounded House Staff training requires the addition of carefully planned and supervised clinical exposure to ambulatory patients for whom the resident shall be a "primary physician," identifiably, with continuing responsibility for that patient's care for a reasonable period of time.

These factors must be weighed in the light of the lifelong precepts of most physicians originally trained traditionally to relegate ambulatory medical problems to the background as the less important and less urgent, and as being unworthy of occupying important time in the precious curriculum for the medical student. Add to that fixed frame of mind of the faculty, the fact that the medical student generally takes his cue from the attitude of his teacher—and the obstacles are many in the path of prompt and significant alteration of the curriculum.

Reordering of Priorities: One Institutional Approach (Beth Israel Medical Center)

Therefore, the first order of business would appear to be to reconstruct and reorder our priorities. If, for the several reasons already listed, it is necessary to train our students and house staff along additional and altered pathways, including ambulatory medicine as an adjunct to the inpatient medicine, there must be a reorientation with a comprehension and commitment toward this end. The Chairman of the Department of Medicine must be committed to the success of his department's tilt in this direction. Lip service alone will not suffice, obviously. In this regard, I quote here a short but amusing verse by Dr. Michael Stewart (12):

Who Goes There?

With teaching hospitals assessing
Care, there's trouble brewing,
Since what professors are professing
Isn't what they're doing:
They speak with growing recognition
Of everyday disease,
And woo the primary physician
To their OPDS—
Common words, although it's rare
To find professors working there.
This problem, focal and systemic,
Probably is academic.

Dozens of titles have been employed to indicate the area of medicine which we are discussing here. The exact phrase matters not. Until a single title is adopted (if ever) for this type of medical care, it is necessary only that we understand what we are talking about, under whatever labeling we feel most comfortable.

Be that as it may, the net from these various considerations at my institution was the conclusion that we must ensure deep understanding and commitment by the Department of Medicine to such an ambulatory health program. Toward that end I accepted the professional appointment as Director of Ambulatory Care for the Beth Israel Hospital, with a continuing bridge in my long-held home in the Department of Medicine. I serve in that key department as Associate Director, for Ambulatory Care. In addition, to underscore the commitment of the Administration to this program, I hold a third (administrative) appointment as Director of Ambulatory Health Services for the

Beth Israel Medical Center, with direct responsibility to the General Director of the Center.

After several months' study we decided that rendering of meaningful outpatient care at house staff level is a more appropriate function for residents than for interns. If this type of patient care by House Staff is to be clinically meaningful and an effective, continuing learning experience, it requires:

1. Resident level experience.
2. More than one resident assigned at one time in the clinic setting.
3. Continuity of patient care by the resident who is clearly identified as the responsible physician.
4. Faculty supervision continuously.
5. Close and contiguous cooperation by the special support services including Gynecology, Psychiatry, Dermatology, Ophthalmology, Otolaryngology and Orthopedics.
6. Planned curriculum and teaching program including conferences and seminars.
7. (as stated): Commitment and involvement by the Department of Medicine, as well as by other respected faculty and administrative personnel.

Such a unit in our Comprehensive Health Services has been arranged for the academic year 1975–1976. It will commence on October 1, 1975 and operate each weekday from 9:00 a.m. to 5:00 p.m. One second or third year house officer (first or second year resident) is assigned to the OPD as his primary and exclusive duty for one month. Another resident (mostly first year) is assigned to each of the 10 weekly half-day periods, repeatedly and continuously throughout the year. These assignments are intended to continue for the duration of his or her house staff service period. We have assigned in code the term "horizontal" to the uninterrupted month's service and "vertical" to the repetitive half-day service. Thus, 11 different persons from the resident staff are in-service each week. The residents are supervised at their work by a full-time faculty member for whom this is a prime duty. A key toward achieving continuity of care for the patients by the same physician is for the resident to "roll over" to a vertical slot immediately after the completion of the first horizontal month. Thereafter, all follow-up appointments will be scheduled for his or her half-day in the vertical assignment.

The logistics are not simple. Allowance may have to be made for certain times in the "vertical" resident's duty periods during which he or she will find it difficult, if not impossible, to attend on the assigned half-day of certain months. Of course, these immediately include vacations and illness. Elective assignments of one or two months at distant hospitals, such as The Mount Sinai Hospital which is a distance of four miles through busy Manhattan from Beth Israel Hospital, might present a barrier but we intend to abide by the principle that no elective or other service period will be reason for excuse from OPD duty. This will also refer to months in CCU or ICU.

The work hours are 9:00 A.M. to 1:00 P.M. and 1:00 P.M. to 5:00 P.M. Conferences and orientation exercises are planned for the 8:00–9:00 A.M. hours, both by the assigned faculty supervisor and the speciality consultants.

The curriculum to achieve a meaningful and effective course in Outpatient Medicine is being composed with the active assistance of the other departments most involved: Psychiatry, Gynecology, Urology, Dermatology, Orthopedics, Allergy and Immunology, Ophthalmology and Otolaryngology.

The clinic workday schedule is shortened only on Thursdays when the staff is freed to attend Medical Grand Rounds at 4:00 p.m. Other formal teaching conferences will be planned for the 8:00–9:00 a.m. hour. The associated personnel in the unit comprise:

1	Faculty supervising physician
1	Head nurse
2	Public health nurses
1	Social worker
1	Nurse practitioner
2	Clinic clerks
1	Typist
2	Nurses' aides

The resident is intended to have one hour for a new patient and to average 20 minutes for a return patient, once he has acquired a roster of returnees. At the start, one new patient per resident will be scheduled for each half-day session, with build-up to two at a maximum, within the limits of his return patient load, including the inevitable walk-ins. It is planned for the Nurse Practitioner to have an active role in handling walk-ins.

The matter of continuity of care concerns all of us. It can be readily envisioned and achieved with the "vertically" assigned residents since they are expected to be back each half day on the same day all of the year (and years) with the probability that only one alternate resident will, on occasion, occupy that slot. This same continuity cannot be so readily achieved with the "horizontal" assignments where, at the least, 12 physicians will be involved (nine for this first year since the take-off is October). We aim to solve this problem, as stated, by "rolling over" the resident into a vertical assignment immediately following his month of horizontal duty.

Several reflections at this point are in order:

1. We propose to study the impact on patient care by each of these two approaches to House Staff care of OPD patients.

2. We hope, in the future, to increase the period of continuous assignment of the horizontal resident to periods longer than one month, by one means or another.

3. Whether horizontal or vertical, a continuing interest in the patient (and perhaps a meaningful relationship, also) can be achieved by the Resident Physician, even when he is working elsewhere. For example, out of hours, the Emergency Room at Beth Israel Hospital has a rolodex file of all Medical Clinic (Comprehensive Health Service) patients with clinical and other pertinent data, including the name of the assigned physician(s). For those patients whose records are already on computer, a read-out with such data is also immediately obtainable. If such a patient appears or telephones, one of these residents can be immediately contacted for care or counsel for this patient, much as any of us who also has some private practice is reached at all hours

and at all places.

4. It is planned, as part of the total care of these patients in the ambulatory setting, to give the resident physician an awareness of the home surroundings of his or her patient. Aside from the obvious boost toward greater mutual understanding and resulting better relationship and care, this identification will serve for ready recall at any time during the year that the patient requires care out of hours—or in clinic-session time.

5. It is intended to study the relative merits of this Resident Clinic and the already existing two Comprehensive Health Service clinics. The latter are comparably composed except that the physicians are at the Attending level and serve full-time periods which ensures continuity of care and identification of the patient with one primary physician.

6. It is expected that the residents will be impressed with the value of this type of patient care and the resulting benefit to their education and training. This will be achieved, in part, by the seriousness with which their teachers view this part of their training period. This serious view and commitment will be made evident to the house staff in every possible and practical way, including:

a. Reminder that this training period is required for their eligibility for the examination of the American Board of Internal Medicine; and that

b. Their evaluation by the Department Faculty Committee for fitness to take that written examination will include, among others, their performance in this ambulatory setting.

c. The devotion of respected faculty staff members to the furtherance of this program (on the premise that such visible and meaningful commitment speaks louder than words alone).

d. The making of the teaching of office medicine attractice and meaningful and, if at all possible, inspiring to Residents. Toward this end, conferences, seminars and case presentations are planned on a regular basis at a prescribed hour.

Conclusions

Many factors and circumstances are combined to pointing up the need for new approaches to rendering health care. In the hospital setting, and particularly where the element of student and house staff training is added, innovative thinking is especially required in an attempt to fulfill all demands. These have been considered. One institution's expanding approach to meet these problems is presented. It is predicated on its existing program for delivery of primary and comprehensive health care in an ambulatory setting to which has been adapted a structured house staff program of clinical service and education, while maintaining the goals of the rendering of comprehensive and continuous health care by primary physicians.

References

1. Logan, A.: Quotation in AMA News, p. 1, June 18, 1975.
2. McDermott, W.: General Medical Care. Identification and Analysis of Alternative Approaches, Johns Hopkins Med J. 135:292–321 (Nov.), 1974.

3. Freymann, J. G.: *American Health Care System: Its Genesis and Trajectory*. Medcom Press, New York 1974, 407 pp.
4. Janeway, C. A.: The Decline of Primary Medical Care: An Unforeseen Consequence of the Flexner Report, Pharos 37:74–80, 1974.
5. Lewis, H. L.: Methodist of Indiana: A Pioneer in Preventive Medicine. Modern Health Care, 21–26, (December), 1974.
6. Berarducci, A. A., Delbanco, T. L., and Rabkin, M. T.: The Teaching Hospital and Primary Care, New Engl J Med 292:615–620, 1975.
7. Petersdorf, R. G.: What Every Young Doctor Should Know, Pharos 38:65–69, 1975.
8. Young, L. E.: Backward and Foward Integration, Arch Intern Med 134:1127–1131, 1974.
9. Almy, T. P.: Primary Care and Departments of Internal Medicine, Arch Intern Med 134:771–773 (Oct.), 1974.
10. Proger, S.: A Career in Ambulatory Medicine, New Engl J Med 292:1318–1324, 1975.
11. Statement adopted by the American Board of Internal Medicine, September 11, 1974: Training and Certifying the Internist for Primary Care.
12. Stewart, M.: Who Goes There? Ann Intern Med 82:706, 1975.

Addendum to New Approaches to Patient Care in the Hospital Setting

August 1, 1976

Since the preparation and delivery of this paper on October 3, 1975, the plan was modified to permit greater numbers of the resident group to participate in this program. The original anticipated total of 11 vertical and horizontal resident physicians was at once exceeded when *all* of the 20 second-year medical house officers expected to be accomodated in this Comprehensive Health Service Unit (naturally named "Unit C" in light of the already existing Units A & B, manned by full-time attending physicians). For reasons of construction, the unit site was not ready before November 10, 1975. The program, nonetheless, was started in October, 1975, with the weekly Monday 8:00 A.M. to 9:00 A.M. seminars covering the commonly encountered areas in Ambulatory Medicine. Following two seminars for organization and orientation, these 35 seminars stressed office management of clinical problems and continued until June 14, 1976. The subjects covered follow:

October 6, 1975	–	Organization and orientation
October 14, 1975	–	Orientation (continued)
October 20, 1975	–	Hypertension
October 27, 1975	–	Diabetes mellitus
November 3, 1975	–	Gynecology
November 10, 1975	–	Dermatology
November 17, 1975	–	Depression, recognition and therapy
November 24, 1975	–	Dietary therapy
December 1, 1975	–	Joint pain (orthopedist's approach)
December 8, 1975	–	Joint pain (from rheumatologist's point of view)
December 15, 1975	–	Ophthalmology
December 22, 1975	–	Depression (continued)
December 29, 1975	–	Respiratory infections
January 5, 1976	–	Menopause. Contraception
January 12, 1976	–	Common thyroid disorders

January 19, 1976 – Principles of wound care
January 26, 1976 – Diabetes mellitus (continued)
February 2, 1976 – Clinical conference
February 9, 1976 – Psychosomatic medicine
February 16, 1976 – Holiday
February 23, 1976 – Low back syndromes
March 1, 1976 – Social work services
March 8, 1976 – Peripheral vascular diseases
March 15, 1976 – Thyroid nodules—Clinical conference
March 22, 1976 – The ENT examination
March 29, 1976 – Menopause
April 5, 1976 – Mouth care
April 12, 1976 – Urology
April 19, 1976 – Diseases of the breast
April 26, 1976 – Acid - peptic disease
May 3, 1976 – Rehabilitation medicine
May 10, 1976 – Breast disease (continued)
May 17, 1976 – Venereal disease
May 24, 1976 – Clinical conference
May 31, 1976 – Holiday
June 7, 1976 – Review of year with Residents
June 14, 1976 – Plans for forthcoming year with new Resident Class

During the eight months when the unit operated, horizontal residents totaled eight, each of whom reverted after the month's assignment to his or her assigned vertical half-day. Since the total Resident complement was 20, this meant that in the same period of eight months 19 residents served during ten half-day sessions each week. The total number of examinations accomplished by this group between November 10, 1975, and June 30, 1976 (= 33.6 weeks including 162 working days) was 2848, including 610 new patients. The total number of residents assigned in these 162 days was 478.5 FTE, which averages 2.9 FTE resident per day. Each resident averaged 6.0 patient examinations per day, including 1.3 new patients seen.

These figures reflect the newness of the resident staff's introduction into the private practice type setting and their relatively lesser production (by number) of patients served when compared to either of the other, longer established, attending-based Units. The time required for examination of a new patient and dictation of a note (in problem-oriented format) consumed up to 1½ or 2 hours at the start, so that in the usual three to four hour stint the Resident at first rarely saw more than one new patient and several returning patients. Team support included an initial (preceding) interview of the patient by a Public Health Nurse and return of the patient to that same nurse following the physician's examination for postexamination conference. Also, the patient was interviewed when indicated by the Social Worker. The Resident's findings on examination of each patient, as well as his management and record, were reviewed immediately or subsequently by the Faculty Supervisor whose omnipresence in the Unit was vital to its operation.

Problems that surfaced in these eight months included:

1. Unavailability of some Residents to attend the Monday 8:00 a.m. seminars because of urgency of weekend turnover rounds. (Therefore arrangement has been made to shift this seminar from Mondays to Fridays, same hour, for the next academic year).

2. Unavailability of some Residents to keep their appointments on their vertical half-days when assigned to the Medical Intensive Care Unit. (This was met judiciously by the Faculty Supervisor, on anticipating this potential conflict, by scheduling no *new* patients for the Resident in that month).

3. Unavailability, in the early months, of some vertical Residents on electives off the immediate Beth Israel campus area. (This was addressed by restating and enforcing the policy that no assignment would lead to excuse from appearing on the assigned half-day, but nonetheless, as with the preceding item, with judicious lightening of the examining load of the resident physician for the month in question. This was accomplished by calling no new patients, and by farsighted appointment scheduling of return patients).

4. Lack of prompt arrival of some vertical Residents when assigned full-time at the Gouverneur Hospital. (This presented occasional difficulty but is no longer a factor since the affiliation with Gouverneur Hospital ended as of July 1, 1976).

The impression thus far of those who have been monitoring the program is that it has fulfilled its goal of effectively introducing these internists-in-training to this aspect of Medicine. From the Residents themselves, the response in these first 8 months has been generally enthusiastic. Most feel it is a worthwhile clinical experience and express pride in their introduction to the private practice setting with all that it implies. The last is underscored by the interest in the patient's welfare during out-of-clinic hours, including admission to the hospital as an in-patient. However, there remains yet to be effected better the elusive goal of meaningfully wedding the out- and inservice care of these patients.

For the coming academic year, the 15 new first-year Residents in Medicine are being added to the program. Six are available for two months assignments as horizontal physicians, nine for one month of such assignment, and all 15 will serve on vertical assignment in the other months. Orientation of this new group was conducted during June, 1976, as was already indicated above.

Following is the calculated percentage of total curriculum time for these two Resident groups that has been or will be spent on Ambulatory Medicine:

> During the year 1975–1976, the Resident group spent 10% of their total curriculum time in the Comprehensive Health Services Unit. (To this perhaps should be added 8.3% of the Resident's curriculum time for assignment to the Emergency Service when one totals curriculum time spent on Ambulatory Medicine). For the coming year, with both the present and the incoming Resident classes, these figures are calculated to be 9.2% in Unit C for the senior resident group, 19.7% for the junior group. To each of these figures can be added 8.3% for Emergency Service, making totals of 17.5% and 28%, respectively.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, March–April, 1977
Printed in U.S.A.

Patient Flow Modeling: A Practical Technique for Ambulatory Care Reorganization*

MICHAEL M. STEWART, M.D., M.P.H., JONATHAN M. METSCH, D.P.H., THOMAS A. REILLY, M.D., MICHELE G. GREEN, M.A., AND JEAN PORTA, M.S.

The proper function of a medical care system or subsystem requires the availability of certain essential resources, including an appropriate range and mix of personnel, equipment, space, and patient care services. However, these resources may be ineffective if they cannot be appropriately utilized by patients who need them, or if patient behavior creates unexpected or unplanned patterns of medical care demand (1).

Lack of proper integration of available resources and patient utilization behavior may cause a variety of problems. For example, patients may fail to keep OPD appointments for special diagnostic procedures, such as radiologic studies or electrocardiograms. In some cases the reasons may be simple, such as inconvenience to patients of a scheduled appointment time. Patients may also be erratic in keeping regularly scheduled OPD clinic appointments, not because of lack of concern for their health, but because of the negative impact of poor physician-patient continuity during previous visits to a clinic (2). These and many other factors may determine patient utilization patterns in a particular setting (3).

In any situation where the structure of a medical care system fails to provide an appropriate match between available resources and the needs of individual patients, two results are likely. First, patients may not receive the proper amount or quality of care. Second, available resources may be poorly utilized. Certain problems of the second type can be resolved when they are clearly understood. This may require the development of special analytic approaches.

This paper describes a problem-solving approach, Patient Flow Modeling, which was developed during the planning of a new appointment system for the General Medical Clinic at City Hospital Center at Elmhurst (Queens, N.Y.). In recent years, this clinic has experienced a heavy patient load, long waiting times within the clinic, and long delays for new appointments and reappointments (4). It was generally recognized that the resources of this clinic were not being optimally utilized. However, no careful study of the types and causes of poor utilization has previously been made.

From the Health Services Research Unit, Department of Ambulatory Care and Community Medicine, Mount Sinai Hospital Services, City Hospital Center at Elmhurst, Elmhurst, N. Y. 11373.

* Supported by a grant from the Commonwealth Fund

Requests for reprints should be sent to: Michael M. Stewart, M.D., M.P.H., Department of Medicine, College of Physicians and Surgeons of Columbia University, 630 West 168 Street, New York, N. Y. 10032.

Some of the problems inherent in the operation of a large outpatient clinic lend themselves to analysis through use of sophisticated techniques, such as queueing theory. However, the first step in the analysis of a complex outpatient flow problem is the development of a sound conceptual model. At the most basic level, the volume of patients seen in any clinic is a function of three factors: the number of new referrals, the number of follow-up visits, and the broken appointment rate. At Elmhurst, it was felt that the first step in analysis of the General Medical Clinic was to develop a conceptual model incorporating the relationships of these three factors with patterns of patient flow through the clinic.

A logical series of questions follows from the application of this conceptual framework:

How many individual patients use this clinic?
How frequently do they use it?
What are the major sources of referral?
What is the overall broken appointment rate?
Do broken appointment rates vary with referral source?
How do these patients use other hospital clinics?

These questions, and others of a more detailed nature, serve a dual purpose: they assist in refining the conceptual model, and they also help to indicate those areas of uncertainty which are most critical in understanding patient flow patterns through the General Medical Clinic.

The Setting

City Hospital Center at Elmhurst (CHCE) is a 900-bed municipal receiving hospital for some 900,000 people in the western half of the Borough of Queens, in New York City. General outpatient care for adults is provided in three areas: the General Medical Clinic (GMC), the Diagnostic Clinic (DC), and the Medical-Surgical Emergency Unit (EU). Operating characteristics of these three adult primary care units are shown in Table I.

For many years, appointments to the GMC have been made according to a "block system," with patients instructed to appear either at 9 A.M. or at 1

TABLE I

Adult Primary Care Services, Elmhurst

	Emergency unit	Diagnostic clinic	General medical clinic
Daily Volume (visits)	200	120	100
Hours of Service	24 hours daily	14 hours, weekdays 8 hours, weekend days	8 hours, weekdays
Appointment System	None	None (walk-in only)	Appointments only
Physician Staff	Salaried internists and surgeons; fixed schedules	Salaried internists; fixed schedules	Salaried internists; fixed schedules
Problems Treated	Emergent and urgent problems Non-urgent problems (when DC closed)	Non-urgent problems Initial diagnostic evaluations	Chronic care problems Diagnostic evaluations
Referrals	To GMC and specialty clinics	To EU, GMC and specialty clinics	To specialty clinics

P.M., when half-day clinic sessions begin. Appointments to the GMC can be made through the EU, DC, or other clinics; from the inpatient services for patients about to be discharged; or from within the GMC itself, for clinic follow-up visits. This appointment system has been coordinated with the Medical Records Department, which is responsible for providing medical records for all patients scheduled to appear for each GMC session.

Problems with this appointment system have been numerous. In addition to long delay times for appointments and long waiting times in the clinic, other problems include: a high broken appointment rate; variable and unpredictable patient load; poor physician-patient continuity on successive clinic visits; and ineffective utilization of physician time. These problems are not unusual. They are characteristic of the types of inadequacies commonly seen in large municipal hospital outpatient systems (5).

At Elmhurst, these problems have suggested the need for a more effective OPD appointment system. Two goals of this system would be to improve resource utilization and to establish a more predictable daily workload. The specific objectives of a new appointment system include the following:

reduce delay for new appointments (less than two weeks)

reduce waiting time after arrival in the GMC (less than one hour)

satisfy patient preferences for appointment by day of week and time of day

develop the capability to make appointments on short notice

improve physician-patient continuity on successive vitits

stabilize sessional, daily and weekly workload (less than 20% variation in number of patients)

increase physician-patient contact time (average 15 minutes for "old" patients, 30 minutes for "new" patients).

Patient Flow Modeling

In order to determine the magnitude and determinants of the problems previously described, a detailed study of the GMC was conducted, including operational relationships of this clinic with other ambulatory care units. Figure 1 illustrates, in schematic form, the analytic model used in this study.

It is important to note that the arrows in Figure 1 can be interpreted as designating groups of patients moving through the system (patient flow), as well as particular characteristics of the different units which affect patient flow. For example, the arrow labeled M can be used to indicate that group of patients which receives appointments for follow-up visits from within the GMC. The same arrow can also be used to designate the proportion of all GMC visits which are follow-up in nature, or the policies determining these follow-up visits. Similarly, the arrow labeled E can indicate both the number of new patients referred from the Emergency Unit within a given time period, or any aspect of the EU-GMC relationship which affects patient flow into the GMC.

This schematic model has proved to be a useful tool for the initial analysis of a broad range of operational problems related to the establishment of a new appointment system in the GMC. Some illustrations of information gathered through use of this model include the following:

Patients seen in the DC and EU may receive GMC appointments for follow-up care. Both EU and DC are given quotas of appointments for future GMC sessions (E, G), with the GMC being notified of the names and total numbers of patients. However, broken appointment rates for patients referred from these two sources are high (40%–70%), as compared to the broken appointment rate for follow-up visits of patients already known to the GMC (25–35%). Indiscriminate mixing of appointments from these different sources causes serious unpredictability in expected GMC workload for any given clinic session.

Many regular GMC users (M) are also frequent users of the DC on a walk-in basis (H), on their own initiative.

Patients referred to the GMC (E, G, I, K) frequently choose to discontinue using the GMC as a source of continuing primary care, and are either seen elsewhere in the hospital by personal choice (F, H) or by receiving appointments to other clinics (J), or are lost to follow-up (L).

Within the GMC itself (A) different physicians require different amounts of time to examine patients, due to a variation in the complexity of patient problems and differences in physician working habits. In a new appointment system, more time is needed for new patients (E, G, I, K).

Many patients regularly use both the GMC (M) and medical specialty clinics (J). In many cases, this represents unnecessary duplication of services or inappropriate use of specialty consultations.

There is a low degree of physician-patient continuity on successive GMC visits (M, less than 50%), partially due to the unpredictable patient load for any given half-day clinic session (50–85 patients).

No formal mechanism currently exists for new or follow-up patients to cancel appointments (E, G, I, K, M). This contributes to unpredictability of patient volume.

This type of analysis of patient flow patterns and clinic characteristics has

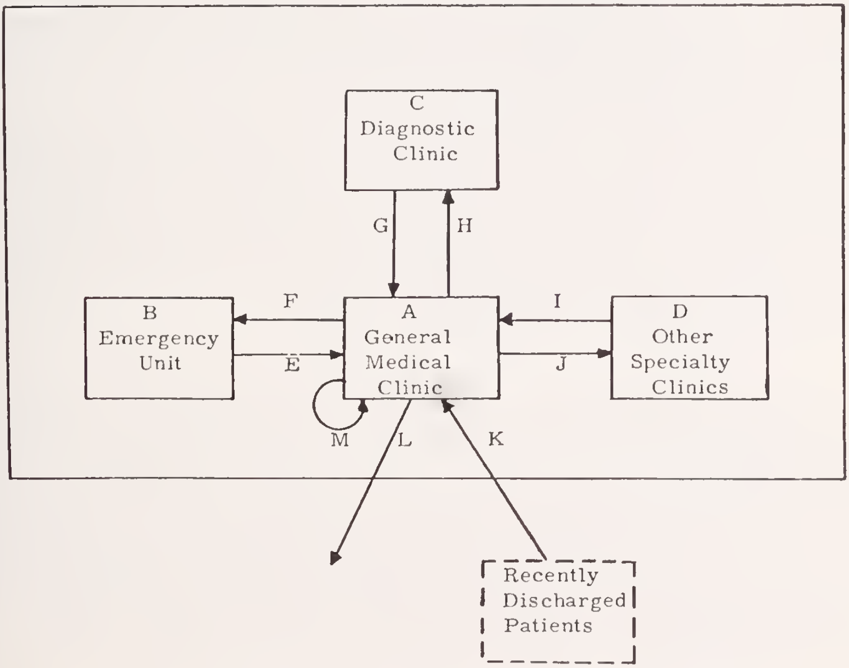

FIG. 1. Patient flow model, Elmhurst General Medical Clinic.

raised the following issues for consideration in planning a new GMC appointment system:

Appointments to the GMC can continue to be made from the EU and DC. However, with known estimates for broken appointment rates for patients referred from specific sources, appointment quota allowances can be made on a more rational basis.

A limited number of appointments for each GMC session could be held open for short-notice appointments for patients previously known to the GMC.

Patients seen in the EU and DC need not be routinely referred to GMC for follow-up of acute of self-limited conditions, unless there are specific additional indications for such referrals. One-visit follow-up mechanisms could instead be established within both the EU and DC.

All GMC physicians should not be expected to see patients at the same pace. Appropriate means and ranges of patient-doctor contact times can be determined for different categories of patients. This information can be used in planning overall GMC workload per clinic session.

Better communications are required between the GMC and medical subspecialty clinics. For most patients, the GMC should provide on-going primary care, with specialty clinics serving primarily a consultative function. Exceptions to this guideline can be negotiated with individual specialty clinics for particular groups of patients requiring continuing clinic care.

A formal GMC appointment cancellation mechanism is needed, so that patients may cancel existing appointments and obtain new ones at the same time.

Future Development of Simulation Models

This initial application of the technique of Patient Flow Modeling in the General Medical Clinic at Elmhurst strongly suggests the potential value of developing computer simulation models for the best use of limited patient care resources within the entire hospital OPD. Sophisticated techniques exist to deal with such questions as: best use of physician time in the various clinics; expectations of numbers and times of patient arrivals; ways to reduce broken appointment rates; and most efficient appointment scheduling methods for patients referred from various sources.

These sophisticated techniques will probably be of greatest value in monitoring the effects of any changes which may be introduced in GMC scheduling, as well as the effects of other efforts to reorganize and improve the ambulatory care system. Continual system readjustments can be made on the basis of changing system characteristics and patient demands, with the objective of achieving greater congruence between the use of available resources and the needs (and demands) of patients.

Discussion

The technique of Patient Flow Modeling is a practical tool with several potential applications. Most important, it can help in establishing an objective conceptual framework for the systematic analysis of how patients actually use specific ambulatory care services. Schematic models, such as that shown in Figure 1, can be adapted for any particular clinic setting. It is likely that the effort required to develop an appropriate patient flow diagram will also help in identifying the important questions which should be asked in any particular setting.

Since the technique of Patient Flow Modeling is a flexible tool, it can be used to illustrate and to clarify clinic relationships, or policies determining such relationships, as well as the volume and types of patient flow between clinics. As mentioned previously, the schematic model shown in Figure 1 was developed from attempts to plan a new appointment system in one clinic at Elmhurst. Similar efforts in OPD planning and reorganization are occurring in many large urban hospitals. It is likely that this conceptual approach will have wider application.

At Elmhurst, it is noteworthy that this approach has led to a critical examination of the objectives, operating characteristics and workload capacity of the General Medical Clinic. The technique of Patient Flow Modeling has helped to determine how best to use available clinic resources in meeting demands for general adult medical care.

Other possible applications of the technique of Patient Flow Modeling should also be mentioned. It could be used to analyze hospital admitting practices, operating room scheduling, and bed control. It could also be used to assess the impact of inpatient care (particularly diagnostic and consultative services) on length of patient stay, or to understand the demand which a home care program places on hospital-based supporting services. While the specific case of GMC appointment scheduling has been the major focus of this report, the technique of Patient Flow Modeling is clearly applicable to many other types of hospital systems planning.

References

1. DeGreene, K. B.: *Sociotechnical Systems*, Chapter 1, Prentice Hall, Inc., Englewood Cliffs, New Jersey, 1973.
2. Hurtado, A. B., Greenlick, M. R., and Colombo, T. J.: Determinants of Medical Care Utilization: Failure To Keep Appointments, Med Care 11:189–198, 1973.
3. Becker, M. H. and Maiman, L. A.: Sociobehavioral Determinants of Compliance with Health and Medical Care Recommendations, Med Care 13:10–24, 1975.
4. Stewart, M. M.: Primary Care in the Large Urban Hospital. Chapter 11 in *Primary Care and the Practice of Medicine*. Edited by J. Noble. Little, Brown and Co., Boston, Massachusetts, 1976.
5. Roemer, R., Kramer, C., and Frink, J. E.: Problems of Fragmented Services. Chapter 8 in *Planning Urban Health Services*. Springer Publishing Co., New York 1975.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

Solitary Neonatal Hepatic Hemangioendothelioma: Case Report and Discussion

CHARLES E. SLOANE, M.D., SE-MIN BAEK, M.D., AND A. ROBERT BECK, M.D.

Abstract

Vascular tumors of the liver in neonates and infants are uncommon and are usually benign. Pathologically, they are classified as hemangioendotheliomas or cavernous hemangiomas, the former being more common. These tumors may cause a variety of potentially lethal complications such as liver replacement, rupture, thrombocytopenia, or high-output congestive heart failure. Hemangioendotheliomas are usually multiple tumors involving both major hepatic lobes and are unresectable. When solitary lesions exist, partial hepatic resection is the treatment of choice and can now be performed in neonates with satisfactory results. One such case is presented. Problems in diagnosis and management are discussed.

Primary tumors of the liver comprise less than six percent of all tumors occurring in neonates and infants (1). Although malignant tumors predominate, benign liver tumors do occur and are often of a cystic or vascular nature (2). Hemangioendotheliomas represent one type of vascular hepatic tumor. Only thirteen of these tumors reported in the medical literature have been solitary (3). We wish to report a successful resection of one such tumor occurring in a neonate.

Case Report

A 3,150 gram female infant was born to a 30-year old primigravid mother at the City Hospital Center at Elmhurst after 38 weeks gestation. Labor and delivery were uneventful. The infant had an Apgar rating of 6 and 9 at 1 and 5 minutes respectively. Shortly after delivery, a firm mass occupying most of the right upper, right lower and left upper quadrants of the abdomen was palpated. The remainder of the physical examination was within normal limits. The hemoglobin was 9.1 gm/100 ml and the hematocrit count was 15.4%. The platelet count was 36,500/cu. mm. Fibrinogen was 160 mg/100 ml (normal 200-400 mg/100 ml), but the prothrombin and partial thromproteins were within normal limits.

Abdominal x-rays showed a homogenous opacity in the right upper quadrant which extended into the right lower and left upper quadrants. Calcifications were not seen. Bowel gas was present only in the left lower quadrant. An intravenous pyelogram revealed intact collecting systems but showed downward displacement of the right kidney (Fig. 1). An abdominal aortogram was performed by inserting a catheter in the umbilical artery. It revealed a large mass with clearly defined margins that occupied most of the right lobe of the liver (Fig. 2A). Tumor vessels were not prominent but venous lakes were seen (Fig. 2B). The interpretation was hemangioma of the right lobe of the liver.

Preoperatively, the infant was transfused to a hematocrit of 45%. On day 11, a laparotomy was performed and a hard mass involving most of the right hepatic lobe and extending to the porta hepatis was found (Fig. 3). The left lobe of the liver was not involved. No other intraabdominal abnormalities were noted. A right hepatic lobectomy was performed.

From the Department of Surgery, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Charles E. Sloane, M.D., Department of Surgery, Mount Sinai School of Medicine, Fifth Avenue and 100 Street, New York, N. Y. 10029.

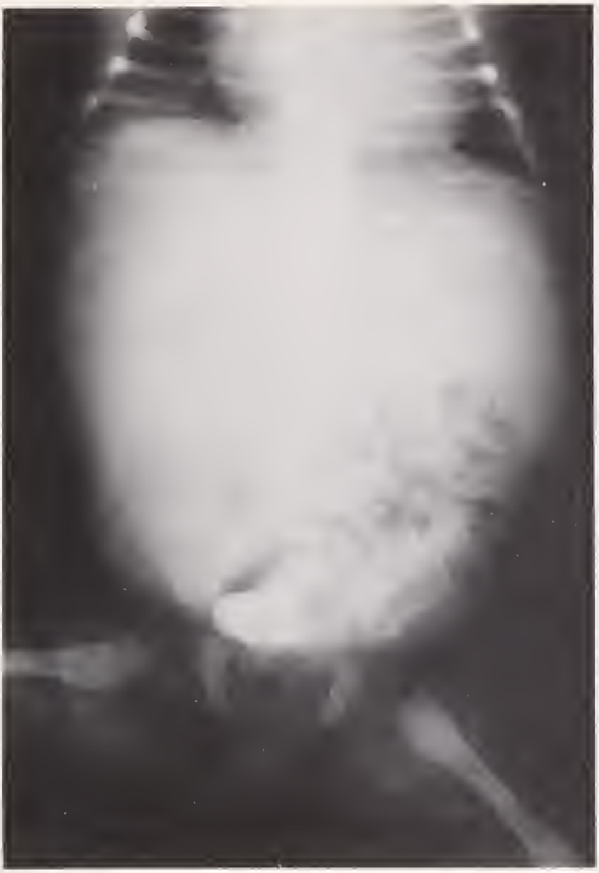

FIG. 1. Intravenous pyelogram showing gas displacement and depressed right renal blush and collecting system.

The tumor measured 10.5 × 4.5 × 4 centimeters. On cross section, the specimen was composed of tumor mass with multiple blood-filled cavities. Microscopically, the tumor showed extensive fibrosis with cavernous vascular spaces and capillary proliferations (Fig. 4). Prominent endothelial cells lined the capillaries. There were recent thrombi in the cavernous vascular spaces. Bile ductules and hematopoietic foci were frequently seen in the stroma of the tumor tissue. The diagnosis was solitary hemangioendothelioma of the liver.

The postoperative course was uneventful. On the first postoperative day the platelet count and fibrinogen level returned to normal and remained so. Bilateral inguinal hernias appeared during hospitalization and were repaired prior to discharge. Follow-up at eleven months revealed the baby to be doing well.

Discussion

Vascular tumors usually occur on mucosal or cutaneous surfaces of the body. Although most vascular tumors are benign, they may cause hemolytic anemia or thrombocytopenia. In general, they have a period of rapid growth or expansion which is followed by maturation, involution and regression. When vascular tumors arise in visceral organs they are difficult to diagnose

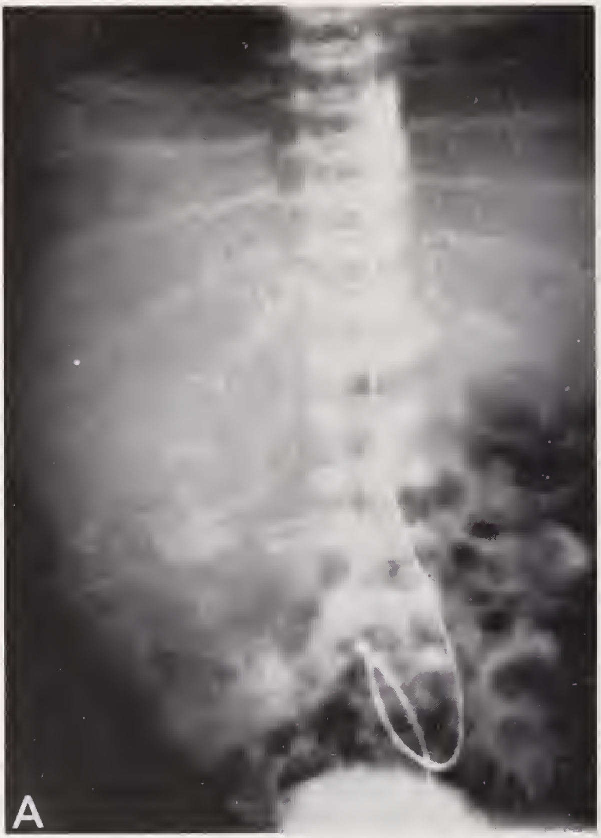

FIG. 2a. Umbilical artery aortogram revealing a large mass occupying most of right hepatic lobe.

and may cause a variety of potentially lethal complications, including visceral compression, congestive heart failure, and tumor rupture with hemorrhage.

Cutaneous hemangioendotheliomas commonly occur in infants in the absence of underlying intraabdominal lesions. Even when both cutaneous and visceral tumors occur, they are unrelated and do not represent metastasis. The cutaneous lesions often regress and completely disappear. Unilateral and bilateral renal agenesis, atrial septal defect, and absent common bile duct are congenital abnormalities that have been reported to occur in infants having hepatic hemangioendotheliomas (3).

Most commonly, vascular tumors of the liver are first noticed on routine physical examination. Some infants present with vomiting, diarrhea, jaundice or abdominal distention (3). Congestive heart failure may be the presenting problem (4, 5). The most notable physical finding is a smooth abdominal mass in the right upper quadrant extending across the midline and downward into the lower abdomen. Jaundice is sometimes present and may be due to liver encroachment or hemolysis. Ascites is very rare (6).

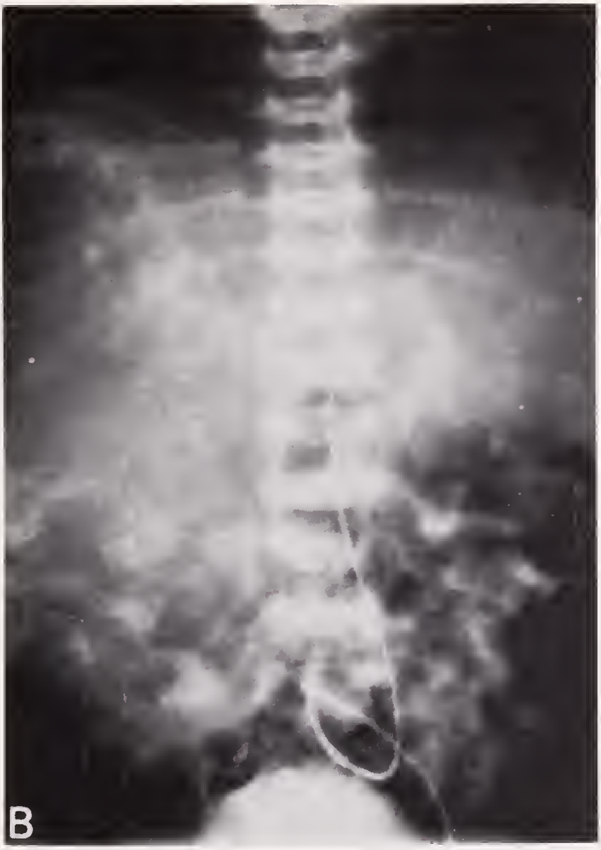

FIG. 2b. Late aortogram film showing venous lakes in the liver.

Laboratory findings are nonspecific. A normocytic, normochromic anemia or thrombocytopenia secondary to platelet trapping within the tumor may be present. Serum bilirubin and liver enzymes may be elevated. Coagulation defects must be corrected if present. The white blood cell count may be normal or elevated depending on the general condition of the infant.

Radiologic examinations are helpful in localizing organ involvement and determining operability. On plain films of the abdomen, a right upper quadrant mass may be seen, sometimes with evidence of calcifications within the tumor. An intravenous pyelogram is needed to differentiate between renal and extrarenal lesions. The chest x-ray may show cardiomegaly. Arteriography following umbilical artery catherization can be performed with ease during the first days of life, and is probably the greatest asset in localization of the tumor and in determing operability. Liver scanning may also be of value.

Vascular liver tumors in infants are either hemangioendotheliomas or cavernous hemangiomas. Approximately 50 hemangioendotheliomas and 10 cavernous hemangiomas have been reported. The diagnosis is usually made

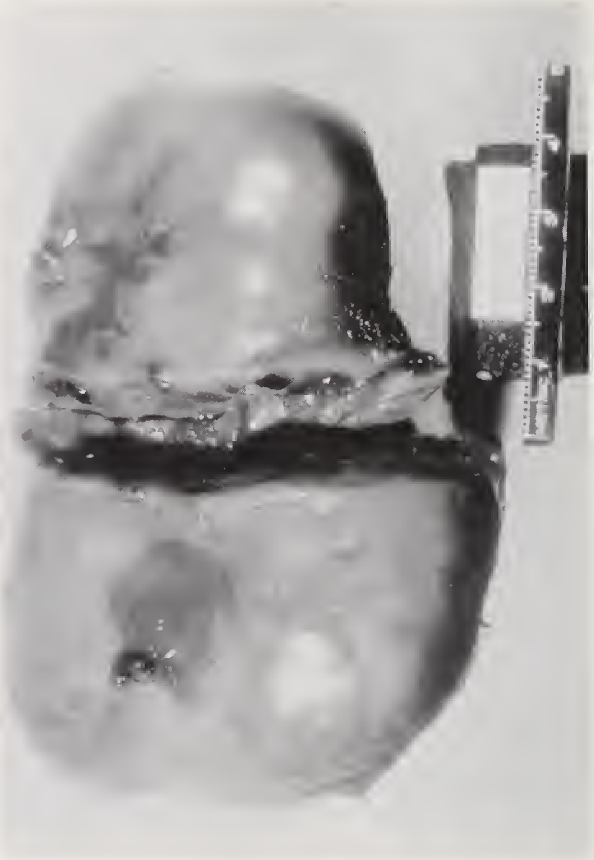

FIG. 3. The resected tumor replacing right hepatic lobe and containing several blood-filled cystic cavities.

before six months of age either by surgical exploration or at autopsy. In some series the sex ratio is equal (3), while in others, females predominate two to one. Caucasions compose about three quarters of all cases.

Hepatic hemangioendotheliomas are usually multiple. Only 13 cases of solitary tumors have been reported (6). They are well circumscribed and nodular but not encapsulated. Solitary lesions are usually hard and of a grayish tan color, while multiple lesions are softer and yellowish red. The tumors range in size from several millimeters to 25 centimeters in diameter.

Hemangioendotheliomas are almost always benign and can histologically be classified into two types (3, 6). Type I tumors are comprised of uniform orderly vascular channels lined by a single layer of regular endothelial cells. The fibrous stroma between the channels is also uniform. Type II tumors have cells which are less uniform and more atypical. Cellular elements are present in greater numbers than needed to form the more tortuous and irregular vascular channels. Actual mitotic figures are rarely seen. At least two truly malignant hemangioendotheliomas have been reported (3). Our patient's tumor has characteristics of Type I.

In untreated cases of hepatic hemangioendothelioma, death usually occurs within six months of diagnosis and is caused by tumor replacement of hepatic tissues. Congestive heart failure secondary to shunting within the tumor may also be fatal. There is a least one documented case of complete regression similar to that seen in cutaneous lesions (3). Several other tumors have partially regressed and, although still present, are asymptomatic.

At present, there is no uniform method of treatment. Hepatic artery ligation (7), steroids, and radiotherapy (8) have been used alone or in combination in isolated cases with random effect. Partial hepatectomy is the treatment of choice in solitary lesions or when multiple foci are present in one lobe; however, hemangioendotheliomas tend to have multiple foci in both lobes. In 1951, Fox performed the first local resection of an hepatic hemangioendothelioma (9). In 1953, Gross reported surgical exploration of 18 primary liver tumors with five partial hepatectomies (10). The only infants to survive were two who underwent exploration and biopsy without resection.

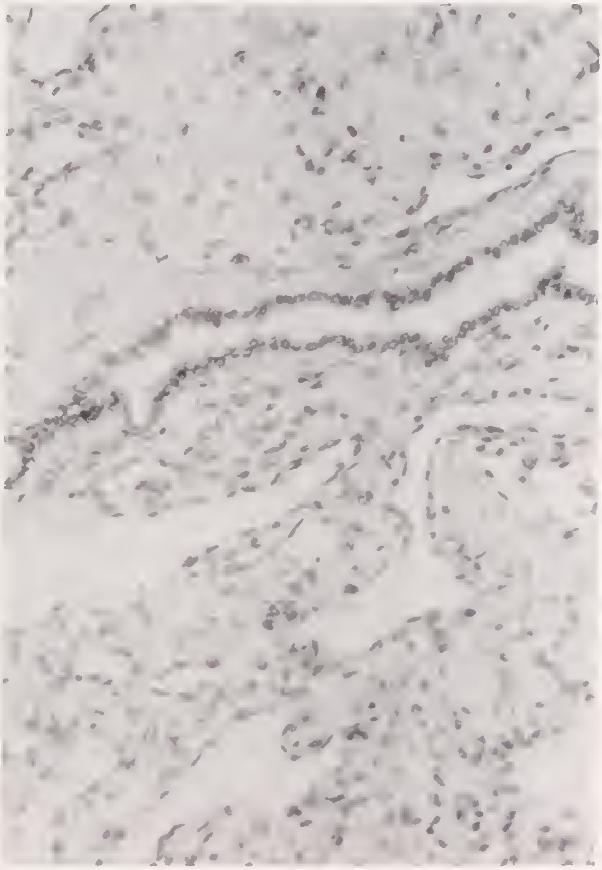

FIG. 4. Microscopic section showing fibrosis, cavernous vascular spaces and capillary proliferation.

However, biopsy of a vascular hepatic tumor without resection is not recommended, as there are four recorded postoperative deaths with this procedure (3). In an early publication, Clatworthy reported two survivors following resection of hepatic tumors (11). As experience broadens, results have markedly improved. Partial hepatectomy is becoming the treatment of choice in benign tumors as evidenced by the fact in his recent series, Clatworthy reports 22 surgical resections of primary liver tumors (12). All patients with benign disease and three of nine patients with malignant disease were alive after five years.

References

1. Keeling, J. W.: Liver tumors in Infancy and Childhood, J Pathol 103:69–85, 1971.
2. Ein, S. H. and Stephen, C. A.: Benign Liver Tumors and Cysts in Childhood, J Pediatr Surg 9:847–851, 1974.
3. Dehner, L. P. and Ishak, K. G.: Vascular Tumors of the Liver in Infants and Children, Arch Pathol 92:101–111, 1971.
4. Leonidas, J. C., Strauss, L., and Beck, A. R.: Vascular Tumors of the Liver in Newborns, Am J Dis Child 125:507–510, 1973.
5. Mattioli, L., Lee, K. R., and Holder, T. M.: Hepatic Artery Ligation for Cardiac Failure due to Hepatic Hemangioma in the Newborn, J Pediatr Surg 9:859–862, 1974.
6. Blumenfeld, T. A., Fleming, I. D., and Johnson, W. W.: Juvenile Hemangioendothelioma of the Liver, Cancer 24:853–857, 1969.
7. DeLorimier, A. A., Simpson, E. B., Baum, R. S., et al: Hepatic Artery Ligation for Hepatic Hemangiomatosis, N Engl J Md 277:333–337, 1967.
8. Crocker, D. W. and Cleland, R. S.: Infantile Hemangioendothelioma of the Liver, Pediatrics 19:596–605, 1957.
9. Fox, P. and Cella, L. E.: Hemangioendothelioma of the Liver, Ann Surg 131:1042–1047, 1951.
10. Gross, R. E.: Miscellaneous Conditions of the Liver and Biliary Passages. In *The Surgery of Infancy and Childhood*. W. B. Saunders, Philadelphia, 1953, pp. 532–535.
11. Clatworthy, H. W. and Boles, E. T.: Right Lobectomy of the Liver in Children, Surgery 39:850–859, 1956.
12. Clatworthy, H. W., Schiller, M., and Grosfed, J. L.: Primary Liver Tumors in Infancy and Childhood, Arch Surg 109:143–147, 1974.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

Hirschsprung's Disease: 25-Year Experience at The Mount Sinai Hospital (New York) and Review of the Literature

JULIO M. SOTO, M.D., ROBIN T. SOTO, ARTHUR H. AUFSES, JR., M.D., MICHAEL BLEICHER, M.D., AND IRWIN H. KRASNA, M.D.

Ninety years have passed since Hirschsprung first presented his classic description of the disease which now carries his name. Following his presentation, a vast amount of literature has accumulated, dealing mainly with problems concerning the origin of the disease. For sixty years this field remained a playground for medical fantasy and philosophy, resulting in numerous theories but few facts. A dramatic change occurred about thirty-five years ago with the recognition of the underlying pathology and with the development of adequate surgical methods of treatment.

Historical Aspects

Harold Hirschsprung (1830-1916) was professor of Pediatrics at the University of Copenhagen, Denmark from 1870 to 1904 and made many essential contributions to pediatrics, such as the first comprehensive reports on pyloric stenosis (1888) and the pioneering use of hydrostatic pressure in the reduction of intussusception (1905). He is best known for his discovery and report of congenital megacolon (1).

A concise translation of relevant parts of his paper would be an appropriate introduction:

"*Constipation in the Newborn due to Dilatation and Hypertrophy of the Colon*

> I venture to present before this expert group two unusual pathological specimens, with summaries of the case reports.
>
> I am going to demonstrate the first specimen right off. As you see this is a colon, but the dimensions are such that you will certainly be astonished to learn that it came from a child which died at an age of 11 months. When the abdomen was opened, an enormously dilated intestinal loop emerged; it was sigmoid and dilated descending colon, while the rectum was not dilated neither was in the site of narrowing. The dilated colon was not only dilated but the muscular walls were greatly hypertropied.
>
> The symptoms provoked by this peculiar disease were:
> progressive unrelenting constipation relieved only by repeated enemas
> frequent abdominal cramps

From the Department of Surgery Mount Sinai School of Medicine of The City University of New York, N. Y. 10029

Requests for reprints should be sent to: Julis M. Soto, M.D.

stools of normal consistency and appearance
child otherwise thriving well on breast milk
as a general rule there was no fever, vomiting was exceptional and appetite was good
spontaneous bowel movements never occurred while unusual abdominal distention occurred."

No definitive opinion was offered as to the origin or pathophysiology of the disease. Hirschsprung offered no therapeutic suggestions. No one knew anything about the disease.

Hirschsprung named this disease Congenital Dilatation of the Colon (1904). Mya originated this term "Congenital Megacolon" 10 years previously (1894) and some years later the name Hirschsprung's Disease came into popular use (2). Hirschsprung's view became known as the malformation theory. Other authorities assumed that dilatation and hypertrophy of the colon were caused by spasm, obstruction, neuromuscular inertness and/or immature colonic development. The Swedish surgeon Lennander (1900) was the first to suggest a neurogenic origin, after multiple exploratory laparatomies showed grossly distended magasigmoid colon in the absence of mechanical obstruction (3). He interpreted the findings as due to deficient innervation of the portion of the colon. Treatment of these patients by repeated electric enemas of the sigmoid was followed by recovery, thus substantiating Lennander's opinion.

In Hirschsprung's disease we are faced with a unique contradiction in findings from gross pathology and microscopy. The defective distal bowel appears normal, while the normal proximal bowel looks dilated (Fig. 1). It is this paradoxical appearance that caused many misinterpretations of the development and life course of the disease. The distal segment, usually denoted as the "narrow segment," is normal or narrow in appearance, and no hypertrophy is found. The transitional zone from dilated to normal or narrow distal bowel is cone-shaped (Fig. 2). Extending proximally, dilatation and hypertrophy usually show a gradual decrease and disappearance (4). The primary lesion in Hirschsprung's disease is the *total* absence of intrinsic ganglion cells from the distal narrow segment (5).

A review of the known facts concerning normal embrylogic development, structural organization and function is essential.

Intestinal motility is dependent on three basic mechanisms—namely automoticity of smooth muscle and its modification under the influence of the intrinsic and extrinsic nerve plexus (6). Any anatomic or biochemical alteration of ganglia, neuroreceptors, or neurotransmitter substances can upset the balance. Experimental studies in chick and human embryos clearly demonstrate that the intrinsic plexus is derived from the craniocervical neural crest (7). Neuroblasts appear in the gastrointestinal tract by migration along vagal trunks, reaching the esophagus and proceeding in a caudal direction. According to Okamoto, neuroblasts are found at the level of the gastric cardia at 6 weeks gestation, at the midgut in 7 weeks, at the midtransverse colon at 8–10 weeks and in the rectum at 12 weeks (8,9). This explains why the distal segment is nearly always involved in Hirschsprung's disease (10). The intrin-

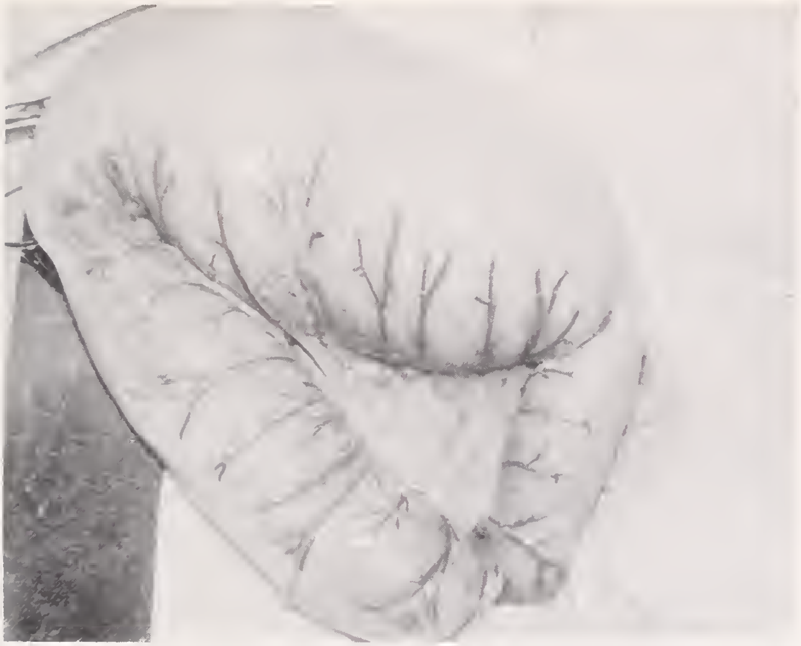

FIG. 1. Typical gross pathology in early stage of Hirschsprung's disease. Photograph at laparotomy in 3-week-old infant, showing moderate dilation of sigmoid colon and normal appearance of aganglionic rectosigmoid. Note moderate disparity. Photography: Dr. Irwin Krasna.

sic plexus is that described by Auerbach & Meissner. Auerbach's plexus, which is formed first, is between the circular and longitudinal muscle layers, while Meissner's only formed secondarily, is spaciously distributed in the loose areolar tissue of the submucosa. Irwin demonstrated that the density of ganglion cells varies at different levels of the gastrointestinal tract (11). Maximum densities are in the pyloric area, the sigmoid colon and rectum (12, 13). The three landmarks used in reporting results of studies in this field are: 1) the internal anal sphincter, 2) the pectinant line (mucocutaneous junction) and 3) the "white line" or Dr. Oh's intersphincteric groove. According to Irwin and Ottaviani the intrinsic plexus can be traced to the level of the internal sphincter where it abruptly ends by sending efferent fibres to the sphincter muscle (11, 14). Numerous studies concluded that the absence of ganglion cells in the internal and external anal sphincter areas should be considered normal (4, 15–20).

A second but inconstant characteristic feature in Hirschsprung's disease is the presence of structurally abnormal hypertrophic nerve bundles between circular and longitudinal muscle layers in aganglionic bowel (21). Increased acetylcholinesterase and norepinephrine concentrations have been well demonstrated in the aganglionic bowel segment. The proximal dilated normal bowel shows hypertrophic circular and longitudinal muscle layers. The transition from normal to aganglionic segments is abrupt and located within the proximal part of the cone-shaped transitional zone. The transitional borders

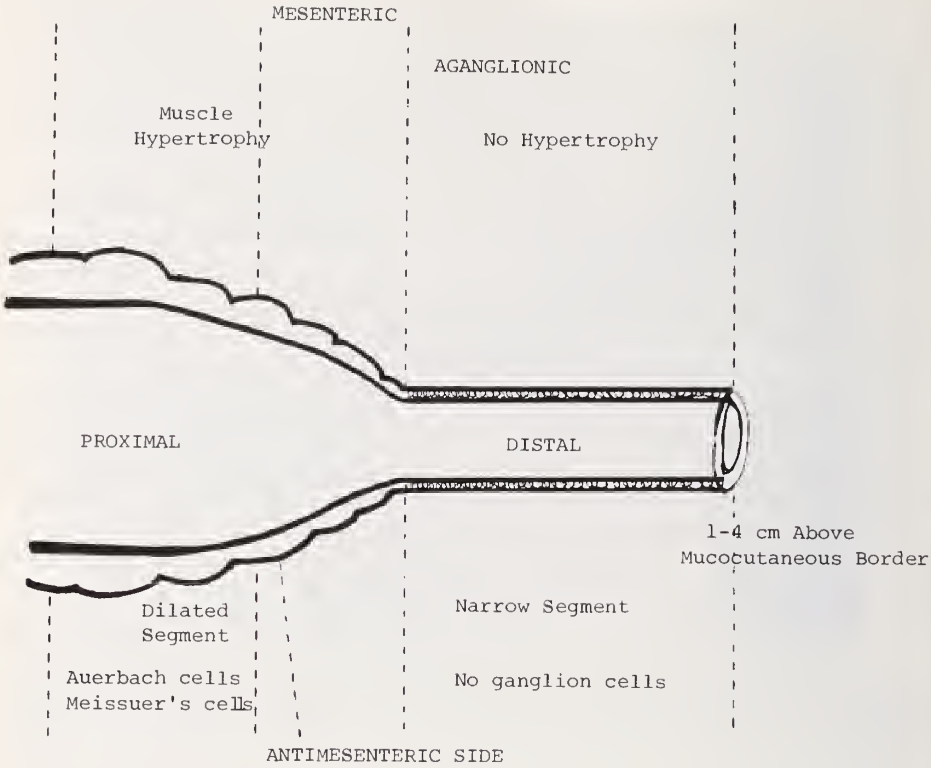
MESENTERIC
AGANGLIONIC
Muscle Hypertrophy
No Hypertrophy
PROXIMAL
DISTAL
1-4 cm Above Mucocutaneous Border
Dilated Segment
Narrow Segment
Auerbach cells
Meissuer's cells
No ganglion cells
ANTIMESENTERIC SIDE

FIG. 2.

are situated more distally on the antimesenteric side than the mesenteric side.

Wyllie in 1957 published a representative series of 152 patients (20, 24–29) (Table I). In 122 of 152 patients (80%) the proximal border of aganglionic segment was located within the rectum or sigmoid colon. Long segment extensive aganglionsis was uncommon and ranged from 8 to 12%.

Intraluminal pressure studies of motility patterns confirmed the absence of propulsive peristalisis in the aganglionic segment while normal recordings were obtained from the proximal ganglionic bowel (30–34). Hiatt noted that the aganglionic segment demonstrated mass contraction without propulsive capacity (31). Canon's law stipulates that smooth muscle is abnormally sensitive to stimuli and tends to contract permanently, as proven by the experiments of Bayliss and Sterling in 1901(35); thus offering a simple and perfectly good explanation of the pathophysiology in Hirschsprung's disease.

Incidence

Hirschsprung and his contemporaries considered congenital magacolon to be extremely rare. Bodian in 1951 estimated one in 20,000 livebirths (36). Three well-controlled series from well-defined dense population areas reveals the figure to be much higher. Madsen (1964) from the Copenhagen area reported 26 cases in 124,000 livebirths; Richman (1966) from the Liverpool region found 157 cases in 150,000 liveborn children while Passarge found 30 cases in 150,000 liveborn children in Cincinnati (37). These results indicate the incidence should be 0.2 per thousand.

It is well estimated that 80% of the patients with Hirschsprung's disease are males. The same male predominance is found in two other diseases probably neurogenic in origin, namely, pyloric stenosis and intussusception. Multiple genetic studies conclude that there is little evidence to support the view of simple Mendelian inheritance (28,38,39). Hirschsprung's disease is a sex-modified multifactorial inheritance disease, in which the threshold of genes needed for expression of the trait is lower in the male (Table II).

Classification and Nomenclature

Prior to the discovery of aganglionisis as the cause of Hirschsprung's disease, the terminology was simple and adequate. A clear distinction was made between idiopathic, congenital, or primary megacolon and secondary megacolon. with the adoption of modern concepts of Hirschsprung's disease, the classification has become more complex (Table III).

There are now two well-defined groups (40). The first group consists of abnormal ganglion cells: that is, their absence (total or subtotal), degeneration, or immaturity. Degeneration or reduction is the pathology caused by Trypanosoma Cruzi in Chagas' disease. Immaturity of ganglion cells must not be mistaken for absence of cells in evaluating rectal biopsies in premature infants (41).

The second group consists of normal ganglionic cells in which symptomatic

TABLE I

Reported Percentage of Colonic Aganglionosis

	Wyllie 1957	Freeman 1957	Bodian & Carter 1963	Walker et al 1966	Rehbein et al 1969
Rectosigmoid	80	88.7	82	82	89.7
Rectosigmoid to descending colon		5.7		4	1.9
Rectosigmoid to left flexure	12	1.7	18	6	4.2
Rectosigmoid to right flexure		1.1			
Total aganglionosis	8	2.8	–	8	4.2

TABLE II

Male/Female Ratios

	Male/Female	
Hirschsprung's disease	3–5 / 1	Bodian et al, 1951: Madsen, 1964
Short segment disease	8 / 1	Gordon et al, 1966; Bodian and Carter, 1963; Passarge, 1967.
Long segment disease	1-4 / 1	Gordon et al, 1966; Bodian and Carter, 1963; Ehrenpreis, 1970.
Total aganglionosis of the colon	1 / 1	Madsen, 1964; Stone et al, 1965; Walker et al, 1966.

TABLE III

Classification of Megacolon

Abnormal ganglion cells	Normal ganglion cells	
Absence	*Mechanism Known*	*Mechanism Unknown*
Hirschsprung's Disease	Symptomatic megacolon	Idiopathic Megacolon
Congenital Megacolon	Secondary megacolon (anorectal strictures, central nervous system disorders, ischemic colitis, ulcerative colitis).	Functional Megacolon
Congenital Aganglionosis		Psychogenic
Hypoganglionosis		Megarectum
Total Aganglionosis		Colonic inertia
Degeneration		Rectal inertia
Acquired megacolon		Colonic constipation
Chagas' disease		*Achalasia*
Anorectal surgery complications		Pseudo-Hirschsprung's Disease
Immaturity		–Segmental dilatation
		(Pseudo-Hirschsprung-Ehrenpreis)
		(Pseudo-Hirschsprung's-Katz)

megacolon is well defined and needs no explanation. Idiopathic megacolon, with its multiple synonyms, forms the bulk of this group. The terms reflects to a large extent the etiology of the condition.

Davidson and Bauer (1958) demonstrated a distal rectal motility pattern characteristic of Hirschsprung's disease although no narrow segment nor aganglionic bowel was noted. This syndrome was called "Achalasia of the distal rectum." Ravitch (1958) coined the term pseudo-Hirschsprung disease rather than using idiopathic (42,43). In pseudo-Hirschsprung's disease the clinical picture is similar but histopathology is normal (44).

Diagnosis

At The Mount Sinai Hospital, the diagnosis, management and treatment of Hirschsprung's disease require early application of two techniques – a barium enema and rectal biopsy. A special technique developed by Neuhauser and Swenson for the demonstration of the narrow segment is almost 100% accurate (30). The keynote in this procedure is that bowel preparation or cleansing enemas should be omitted since they would deflate the bowel, minimizing the diagnostic difference between dilated and narrow segments. The main principle is to instill barium *slowly under fluoroscopy*. As soon as transition into dilated bowel is observed the flow is stopped. Lateral and oblique x-rays are usually best suited to demonstrate the transitional zone. The barium flow is then restarted to demonstrate the extent or degree of colonic dilatation.

It is important to take rectal biopsies from appropriate levels; in newborn children there is an inconclusive zone about 1 cm from the mucocutaneous border while in older children biopsy must be performed at least 4 cm from the mucocutaneous border. In this institution, the Swenson-Fisher technique is the most widely utilized biopsy method (45–47). Under general anesthesia and following sphincter dilatation, the lateral rectal walls are pulled downward by traction sutures; a 1 × ½ cm section is taken which includes circular and longitudinal muscle layers and some areolar tissue. The defect is closed by double rows of interrupted sutures. Duhamel suggests taking full-thickness specimens in performing anorectal myotomy for diagnostic and therapeutic purposes. In England, submucosal biopsy has been widely accepted as easier to perform and equally reliable. Short trials at Mount Sinai Hospital in conjunction with the Swenson-Fisher technique proved them to be less satisfactory. Punch biopsy of rectal valves have been suggested but have proven to be unreliable in our hands (48). As with any surgical procedure, rectal biopsies are not without risk. Fisher and Swenson reported one mortality (cardiac arrest secondary to laryngospasm), one gross hemorrhage and one rectovaginal fistula in 214 rectal biopsies (49). To date out of more than 150 biopsies performed at The Mount Sinai Hospital, no complications have been reported. When there is any doubt about the extent of the aganglionic segment, frozen sections are carried out at laparoscopy to determine the adequate level of colostomy or resection.

Treatment

The main goal of preliminary treatment is to achieve relief from intestinal obstruction. In the newborn, digital rectal examination or a small enema may be sufficient to provoke expulsion of gas and fecal matter. Later on, more vigorous measures are needed.

At The Mount Sinai Hospital, intestinal irrigation, removal of fecal impactions and colostomy are the three main pillars of preliminary management. Irrigations should be carried out using only isotonic solutions (usually physiologic saline) otherwise serious water intoxification will follow quickly; the prominent signs and symptoms are nausea, vomiting, convulsion, and coma. If uncorrected or unrecognized water intoxication may lead to death. Treatment consists of giving hypertonic saline and/or 15% mannitol intravenously. A dreaded complication of Hirschsprung's disease is the development of enterocolitis, that is, more than just the inability of the patients to cope with acute infections such as gastroenteritis; it also involves colonic inability to handle water and electrolytes adequately, since the colon is essentially transformed into a closed loop. Frazer and Berry (1967) postulated that Shwartzman-like sensitivity reaction occurred; that is, intraluminal bacteria released antigens invading the submucosa and causing autoimmunization (50).

Surgery

In 1948, Swenson pioneered a radical change in the treatment of Hirschsprung's disease by the introduction of rectosigmoidectomy (51,52). Swenson's operation offered a logical answer to the problems of this disease. The rationale for removal of the obstructing narrow segment of bowel, restoration of intestinal continuity, and preservation of anal sphincteric was quickly and universally accepted. All presently available surgical approaches to Hirschsprung's disease are, in essence, modifications of Swenson's procedure.

TABLE IV

Results of Swenson's Operation, Including Modifications by Swenson and Grob

Author/year	Cases	Deaths		Early complications			Late complications			
		Early	Late	Incomplete resection	Leak	Stricture	Constip.	Diarrhea	Incontinence	
									Anal	Urinary
Swenson/1957	200	6	7	1	5	9	1	4	0	0
Wyllie/1957	152	6	3	3	9	7	34		41	15
Hiatt/1958	67	1	4					4	9	
Langer and Thompson/1959	22	2	0	1	6	5	3			
Genton & Vontobel/1960	32	1	1			4	8	2	7	5
Hallenbeck et al/1961	34	1	3		9		3	4	2	
Ehrenpreis/1961	69	3	1	6	5	7	5	18	8	7
Kostia/1962	28	0	3	2	7	6	3		2	
Clausen & Davis/1963	34	3	0	1	4	4	6	9	0	
Madsen/1964	77	4	2	8	12	10	12	9	12	8
Swenson/1964	32[a]	0	0	?	0	0	0	8	0	0
Nixon/1966	71	5								
Louw & Cywos/1967	40[b]	2	1							
Fretheim & Knutrud/1967	22[c]	3	0	2			4			
Dorman et al/1967	31	2	1	5	6	1	7	5	8	0
Krasna et al/1976	17[d]	1	2	1	0	1	1	3	1	0
Total	928	40	28	30	63	54	87	66	90	30
				652	664	662	718	593	724	578
Percentage		4.3	2.9	4.5	9.7	8.1	12.3	7.2	12.3	5.3
		7.2								

[a] All patients treated according to Swenson's modified technique.

[b] 12 patients treated according to Swenson's modified technique.

[c] 13 patients treated according to Grob's modification of the Swenson technique.

[d] 17 out of 69 patients with Hirschsprung's disease treated at Mount Sinai Hospital (unpublished data).

Swenson's technique consists of identification of the transitional zone and transection at a level 10 cm proximal to that zone. When in doubt about the presence of ganglion cells, multiple frozen sections are taken at the proximal resection border. Subsequent steps include identification of the ureters and circumferential dissection of the rectum down to the internal sphincters. After defining the aganglionic segment, a trans-anal perineal pull-through is carried out. The everted rectal stump is split 2 cm from the mucocutaneous margin; the colonic stump is delivered through the perineum and anastomosis is carried out at the previously identified area approximately 10 cm from the transitional zone. The following points are stressed by the Pediatric Surgical team at Mount Sinai Hospital.

1. Resection should be deferred until a weight of 30 lbs. is attained. Therefore, in nearly all cases the procedure is staged (preliminary colostomy) to achieve better results.
2. The extent of the resection is confirmed by frozen section at the proximal line of resection by an experienced pathologist.
3. In order to prevent pelvic nerve damage, peri-rectal dissection should be performed sharply and close to the rectal wall—a tedious and time-consuming procedure.

4. Mobilization of the proximal colon should satisfy two important criteria, viz., anastomosis without tension and an adequate blood supply.

In more than 400 cases, swenson observed postoperative enterocolitis in 2% of the patients; this complication was traced to residual obstruction, for which a partial sphincterotomy was included in the primary procedure (53). This sphincterotomy was performed in a way that preserved 1.5–2.0 cm of anal sphincter anteriorly and 1 cm or less posteriorly. In a subsequent modification by Grob, anterior rectal dissection was omitted and posterior dissection carried down to 1 cm from the muco-cutaneous junction, where an oblique anastomosis was performed (54). Another modification was introduced to minimize anastomotic leaks. The everted anal cuff and pulled-through colon were left exteriorized for two weeks, allowing sealing-off of the space between the two bowel segments. Subsequently, resection and anastomosis were carried out.

Endoanal and endorectal pull-though procedures are essentially modifications of the temporary pull-through maneuver (40). The incidence of leak is virtually reduced to zero with these methods. In short, in the endoanal pull-through the anal mucosa is stripped and the rectum is not everted. In the Soave procedure or endorectal pull-through in order to avoid damage to the extrinsic pelvic nerves and muscles of the pelvic floor, pelvic dissection is omitted (55). After coring out the mucosa, a seromuscular rectal cylinder is prepared and the colon is pulled through. Anastomotic leaks were reduced to less than 3% (40) compared to previous experiences (8–12% in Hirschsprung's disease, 10–15% in familial polyposis and 32–50% in Chagas disease). It constitutes at present the procedure of choice at The Mount Sinai Hospital.

It is debatable whether Duhamel's technique should be called a modification of Swenson's procedures or a new method. Duhamel himself feels that it is a technical variation of Swenson's operation (56–59). The Duhamel procedure offers the following advantages:

early resection
no need for preliminary colostomy
low mortality (less than 3%) and
intact innervation and preservation of sensory receptors
prevention of anastomotic leak/strictures
elimination of the obstruction

The principles of the Duhamel procedure are:

minimal pelvic dissection
omission of sutured colorectal anastomosis
the preservation of the anterior rectal wall.

The initial steps in this technique are the same as in Swenson's procedure. Resection of the distal sigmoid is carried out followed by closure of the rectal stump and of the colonic stump 10 cm above the transitional zone. Pelvic dissection is then limited to the posterior rectal half where it is easily carried out in the loose areolar tissue down to the internal sphincter. The mucocutaneous junction is therein incised posteriorly.

In the Swenson procedure, the sigmoid stump was delivered transanally, while in Duhamel's technique the colonic stump is delivered behind the rectum at the posterior muco-cutaneous junction. The colonic stump is then amputated and the posterior limb is anastomosed to the muco-cutaneous junction. The posterior rectal wall is then crushed to the anterior colon wall by Kocher clamps. The clamps fall off after 5–10 days during which time sloughing occurs.

According to Duhamel, the anterior or rectal wall of the resulting neorectum provides for sensory reception and the posterior colonic wall for motility. Multiple postoperative barium enemas support this observation. The Duhamel Pouch fills well and empties adequately.

Because of the soiling problem caused by Duhamel's original procedure modifications were carried out by Grob and Duhamel to preserve the anal sphincter by sparing the muco-cutaneous junction and leaving 1–2.5 cm of sphincter (40). Another method involves the elimination of most of the rectal pouch by crushing a larger portion of the colorectal septum.

Another less popular procedure is State's anterior resection in which 6–10 cm of rectum are left behind and an intraabdominal anastomosis is carried out. This procedure applied to 16 patients requires postoperative periodic bouginage (60).

Results and Comparisons

At present, results from over 1000 Swenson procedures, 400 original or modified Duhamel operations, and 200 pull-through procedures have been reported. On the whole, the results of surgical treatment have been excellent irrespective of the type of operation applied.

The results of Swenson's original and later modified operations are shown on Table 4. Early postoperative mortality was higher than that occurring later. The overall mortality was reduced substantially after 1964 (from 7.2 to 3.5%).

Anastomotic leaks were the most common early complications and accounted for one-half of the postoperative deaths. The clinical manifestations of leaking anastomosis occurred between the 4–10th day after surgery and were associated with fever and occasionally wih peritonitis. Prompt recognition and treatment by draining the retrorectal space (posterior incision with removal of coccyx) and diverting colostomy must be carried out.

Staged operations had the lowest incidence of leaks and practically no mortality. These results strongly suggest the need for a preliminary colostomy (Fig. 3). At The Mount Sinai Hospital, preliminary colostomy is an established rule of preliminary treatment.

The incidence of strictures (almost always due to anastomotic leaks) was similar to that of suture-line disruptions. Here again the protective effect of colostomy should be empahsized. Incomplete resections could be traced to erroneous interpretation of frozen sections at the proximal margin of resection.

Among the long-term complications, obstructive diarrhea and constipation could be attributed to residual mechanical obstruction. Sphincterotomy resulted in improvement of 50–75% of these patients (53). Urinary incontinence was usually the consequence of damage of the anatomic pelvic nerves during perirectal dissection.

An analysis limited to 101 patients indicated that the Soave endorectal pull-through technique appears to be superior to the Swenson procedures in reducing mortality, anastomotic disruptions and strictures (Table 5). The incidence of postoperative constipation and diarrhea was also significantly lower when compared to Swenson's procedures. As previously stated, it is presently the procedure of choice at the Mount Sinai Hospital.

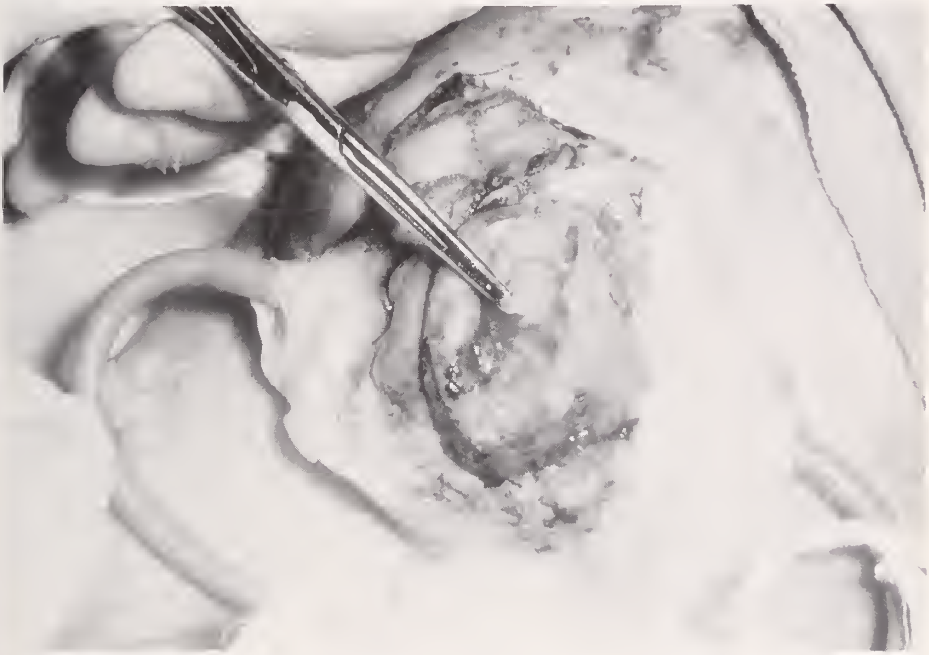

FIG. 3. Colostomy has become a cornerstone of preliminary treatment of Hirschsprung's Disease at The Mount Sinai Hospital.

TABLE V

Results of Endorectal Pull-Through Procedures

Author/year	Cases	Deaths		Early complications			Late complications			
									Incontinence	
		Early	Late	Incomplete resection	Leak	Stricture	Constipation	Diarrhea	Anal	Urinary
Soave/1966	34	2			0	0	1	1	0	0
Nixon/1966	9	1								
Ducharme/1966	7	0			1	1				
Lilly et al/1967	10	0	0	0	1	0	0	2	0	0
Boley et al/1968	13	0				1	1			
Krasna et al/1976	28[a]	0		0	1	1	1	1	0	0
Total	101	3		0	3	3	3	4	0	0
Percentage		3	0	0	3	3	3	4	0	0

[a] Unpublished data. 28 out of 69 patients treated at Mount Sinai Hospital.

The Soave Endorectal pull-through procedure compares very favorably with the Swenson procedure, the mortality rate being 3.4% (Table V). Most important, the early complication rate of leaks and stricutres in 2.0%, as compared is 8% in the Swenson precedure. Constipation is a miniscule 3% (Swenson 17.3%) and Diarrhea 4% (Swenson 7.2%). The main drawback is that only 101 patients have so far been analyzed (40).

Ease of performance is one of the hallmarks of the Duhamel procedure. The most difficult and time-consuming part of Swenson's precedure, that is, rectal dissection, is eliminated or limited to the retrorectal areolar space. This reflects greatly in the operative time saved and probably in the mortality rate. Swenson's procedure takes from 3–6½ hours; Duhamel takes from 2½–5½ hours, a saving of from 2–3½ hours.

The results of Duhamel's operation and modifications were a total of 6 deaths in 366 patients for an early mortality rate of 1.7%, a late mortality rate of 1.1% with an overall mortality rate of 2.8% as compared to Swenson's 7.2% (Table 6) (40).

The early complication leak rate is 6% and strictures occurred in 10% of the patients.

TABLE VI

Results of Duhamel's Operation, Including Modifications

Author/year	Cases	Deaths		Early complications				Late Complications		
		Early	Late	Incomplete resection	Leak	Stricture	Pouch	Constipation	Diarrhea	Anal Incontinence
Forshall/1962	19^{a}	0	0	0	0	0	0	0		0
Kostia/1962	26^{a}	1	0	0	0	4		4	0	10
Sieber/1963	18^{a}	0	0	0	0	0	2	2	1	0
Duhamel/1964	$37^{a,b}$	1	1			2				2
Lynn/1964	10^{b}	0	0		2	1	0			0
Nixon/1966	15^{a}	1	(2 controlled, 12 cured)							
Fretheim/1967	27^{c}	0	0			5	0	5		0
Louw/1967	$40^{a,b}$	2	1	(5 early complications, 3 persistant dysfunction)						
Dorman/1967	30^{c}	0	0	0	3	0	4	2	0	6
Martin/1967	16^{d}	0	0	0	1		0	2	0	0
Ikeda/1967	31^{d}	1	1		0	1	0	1	1	0
Miller/1967	12^{d}	0	0		0	0	0			
San Luis/1968	27^{c}	0	1	0	2	3	2	1	1	1
Ehrenpreis/1966	$51^{a,b}$	0	1	0	4	12	15	1	8	2
Krasna/1976	16^{e}	0	0	0	0	1	0	1	1	0
Total	368	6	5	0	12/193	29/297	23/250	19/254	15/215	21/301
Percentage		1.7	1.5	0	10		9	7.5	7	7
		2.8								

[a] Duhamel's original procedure.

[b] Duhamel's modification.

[c] Grob's modification of Duhamel's procedure.

[d] Rectal pouch elimination.

[e] Unpublished: 16 out of 69 cases with Hirschsprung's disease treated at Mount Sinai Hospital.

TABLE VII

Synopsis of Mortality and Complication Rates after Surgical Treatment

Procedure	No.	Mortality		Complication Rates							
		Early	Late	Incomplete Resection	Leak	Stricture	Rectal pouch	Constipation	Diarrhea	Incontinence	
										Anal	Urinary
Swenson	918	4.3 7.2 2.9		4.5	9.7	8.1	0	12.3	7.2	12.3	5.3
Duhamel	368	1.7 2.8 1.1		0	6.2	10	9	7.5	7	7	0
Ant. Res.	217	2.3 6.4 4.1		–	0.5		0	10.0	0.5	0	0
Endorect. (Soave)	101	2.9 2.9 0		0	3.0	3.0	0	3.0	4.0	0	0

TABLE VIII

The Mount Sinai Hospital Summary, 69 Cases

Procedure	Cases	Mortality		Complication rates							
		Early	Late	Incomplete resection	Leak	Stricture	Rectal pouch	Constipation	Diarrhea	Incontinence	
										Anal	Urinary
Swenson	17	1	2	1	0	1	–	1	3	1	0
Duhamel	16	0	0	0	0	1		1	1	0	0
Endorectal (Soave)	28	0	0	0	1	1	–	1	1	0	0
Preliminary colostomy	48	6[a]	0	–	–	–	–	–	–	–	–

[a] 5 of 6 patients died of severe enterocolitis before definitive procedure attempted.

Constipation, diarrhea and anal incontinence are related to the amount of sphincter left behind. Appropriate measures should be taken accordingly.

A comparison of Swenson, Duhamel, State (anterior resection) and Soave (endorectal pull-through) procedures (Table 7) reveals the mortality rate to range from 2.8% to 7.2%. Incomplete resection was the most common complication before 1965; presently the percent is approximately 1–2% in most recent series. The stricture, constipation, diarrhea and incontinence rates are below 3%. Table 8 summarizes the Mount Sinai Hospital experience.

Summary and Conclusion

Although the surgical treatment of choice can vary from center .to center, the medical and surgical management of Hirschsprung's disease offers an excellent change of complete cure with a minimal incidence of morbidity and mortality (61, 62, 63). Irrespective of the surgical treatment of choice the mortality rates have been.reduced from 80–95% during Hirschsprung's era to 2–7% at present. This great advancement is due mainly to early definitive diagnosis, rapid treatment and prompt surgical intervention at the most opportune time.

Acknowledgment

I would like to acknowledge and thank the following surgical attendings for use of their case material: Drs. A. Robert Beck, Irwin H. Krasna, Daniel Luger, Keith M. Schneider, Jerrold M. Becker, and Michael Bleicher

References

1. Hirschsprung, H.: Stuhltragheit Neugeborener in Folge von Dilatation und Hypertrophic des Colons, Jahrb. Kinderh. 27:1, 1887.
2. Mye, C: Due osservazioni di dilatazione ed ipertrofia congenita del colon, Sperimentare 48:215, 1894.
3. Lennander, K. G.: Fall av medfodd (?) dilatation och hypertrofi av flexura sigmoidea nos ett barn (maladie de Hirschsprung!), Nord, Med. Ark. 11:1, 1900.
4. Bodien, M., Stephens, F. D., and Ward, B. L. H.: Hirschsprung's disease and Idiopathic megacolon, Lancet 1:6, 1949.
5. Whitehouse, F. R., and Kernohan, J. W.: Myanteric plexus in congenital megacolon, Arch. Int. Med. 82:75, 1948.
6. Baumgarten, H. G., Holstein, A. F., Stelzner, F.: Nervous elements in the human colon of Hirschsprung's Disease. Virchows Arch. (Pathol. Anat.) 358:113–136, 1973.
7. Yntema, C. C., and Hammond, W. S.: Origin of intrinsic ganglia of trunk viscera from vagal neural crest in chick embryo, J. Comp. Neurol. 101:515, 1954.
8. Okamoto, E.: Neuropathological and embryological studies on the etiology of aganglionic megacolon, Med. J. Osaka Univ. 13:285, 1961.
9. Okamoto, E., and Ueda, T.: Embryogenesis of intramural ganglia of the gut ant its relation to Hirschsprung's disease, J. Pediat. Surg. 2:437, 1967.
10. Frigo, G. M., Deltacca, M., Lecchini, S., et al. Some observation on the intrinsic nervous mechanism in Hirschsprung's disease, Gut, 14:35, 1973.
11. Irwin, D. A.: Tha anatomy of Auerbach's plexus, Amer. J. Anat. 49:141, 1931.
12. Storsteen, K. A., Kernohan, J. W., and Bargen, J. A.: The myenteric plexus in chronic ulcerative colitis, Surg. Gynec. Obstet. 97:335, 1953.
13. Kotarle, F.: Chagas' disease—its pathogenesis and significance as an epidemic, Z. Tropenmed. Parasit. 10:236, 1959.
14. Ottaviani, G.: Histologisch-anatomisch Untersuchungen Ober die Innervation des Mastdarmas, Z. Mikr. Anat. Forsch. 47:151, 1940.
15. Stelzner, F.: Kontinenz, Superkontinenz und Inkontinenz im Anorectalbereich, Deutsch. Med. Wschr. 90:2275, 1965.
16. Holmes, A. M.: Observations on the intrinsic innervation of the rectum and anal canal, J. Anat. 95:416, 1961.
17. Kiesewetter, W. B., Kukarochana, K., and Sieber, W. K.: The frequency of aganglionosis associated with imperforate anus, Surgery 58:877, 1965.
18. Magnus, R. V.: The folds of Houston in infancy and childhood, J. Pediat. Surg. 2:431, 1967.
19. Alamowitch, C., Gubler, J. P., and Roujeau, J.: L'innervation du sphincter lisse de l'anus, Arch. Anat. Path. 14:28, 1966.
20. Aldridge, R. I., and Campbell, P. E.: Ganglion cell distribution in the normal rectum and anal canal. A basis for the diagnosis of Hirschsprung's disease by anorectal biopsy, J. Nediat. Surg. 3:475, 1968.
21. Gherardi, G. J.: Pathology of the ganglionic-aganglionic junction in congenital megacolon, Arch. Path. (Chicago) 69:520, 1960.
22. Gannon, B. J., Noblett, N. R., Burnstock, G.: Adrenergic innervation of bowel in Hirschsprung's disease. Br. Med. J. 3:388, 1969.
23. Wyllie, G. G.: Treatment of Hirschsprung's disease by Swenson's operation, Lancet 1:850, 1957.
24. Bodian, M., and Carter, C. O.: A family study of Hirschsprung's disease. Ann. Human Genet. 26:261, 1963.
25. Walker, A. W., Kempson, R. L., and Ternberg, J. L.: Aganglionosis of the small intestine, Surgery 60:449, 1966.
26. Rehbein, F., Morger, R., Kundert, J. G., and Meier-Ruge, W.: Surgical problems in congenital megacolon (Hirschsprung's disease), J. Pediat. Surg. L:526, 1966.
27. Freeman, N. V.: Long segment Hirschsprung's disease, Proc. Ray. Soc. Med. 64:378–380, 1971.
28. Madsen, C. M.: *Hirschsprung's Disease,* Copenhagen, Munksgeard, 1964.

29. Ehrenprais, T. "Long-term results of rectosignoidectomy for Hirschsprung's disease, with a note on Duhamel's operation, Surgery 49:701, 1961.
30. Swenson, O., Neuhauser, E. B., and Pickett, L. K.: New concepts of etiology, diagnosis and treatment of congenital megacolon (Hirschsprung's disease), Pediatrics 4:210, 1949.
31. Hiatt, R. B.: Pathologic physiology of congenital megacolon, Ann. Surg. 133:313, 1951.
32. Davidson, M., Sleisenger, M. H., Steinberg, H., and Almy, T. P.: Studies of distal colonic motility in children. III. The pathologic physiology of congenital megacolon (Hirschsprung's disease), Gastroenterology 29:803, 1955.
33. Howard, E. R.: Hirschsprung's Disease: A review of the morphology and physiology. Post Grad. Med. J. 48:471, 1972.
34. Imamura, K., Yamamoto, M., Sato, A., et al.: Pathophysiology of Anganglionic Colon Segment: an experimental study of aganglionosis produced by a new method in the rat, J. Ped. Surg. 10:6:865, 1975.
35. Bayliss, W. M., and Starling, E. H.: The movements and innervation of the small intestine, J. Physio. 26:125, 1901.
36. Bodian, M., Carter, C. O., and Ward, B. C.: Hirschsprung's disease, Lancet 260:302, 1951.
37. Ehrenpreis, Th.: Mortality in Hirschsprung's disease in infancy, J. Pediat. Surg. 2:569, 1967 (a).
38. Passarge, E.: The genetics of Hirschsprung's disease. Evidence of heterogenous etiology and a study of sixty-three families, New Eng. J. Med. 276:138, 1967.
39. Gordon, H., Torrington, M., Louw, J. H., and Cywes, S.: Genetical study of Hirschsprung's disease, South African Med. J. 40:720, 1966.
40. Ehrenpreis, Th.: *Hirschsprung's Disease*. Chicago Year Book Medical Publ. Inc. 1970.
41. Meier-Ruge, W.: Hirschsprung Disease. Its astiology, pathogenesis and diff. diagnosis. Curr. Top. Path. 59:131–75, 1974.
42. Ravitch, M.: Pseudo-Hirschsprung's disease, Ann. Surg. 147:781, 1958.
43. Ravitch, M.: In Discussion, Seminar on pseudo-Hirschsprung's disease and related disorders. Arch. Dis. Child. 41:153, 1969.
44. Boley, S. J., The Pathophysiology of H.D. A continuing search, Journal of Ped. Surg. Vol X:861–863.
45. Swenson, O., and Fisher, J. H.: Hirschsprung's disease during infancy, Surg. Clinc. N. Amer. 36:1511, 1956.
46. Swenson, O., and Fisher, J. H.: Hirschsprung's disease in the newborn, Arch. Surg. 79:987, 1959.
47. Swenson, O., and Bill, A. H.: Resection of rectum and rectosigmoid with preservation of the sphincter for benign spastic lesions producing megacolon; an experimental study, Surgery 24:212, 1948.
48. Schandling, B.: Punch biopsy of the rectum for the diagnosis of Hirschsprung disease. J. Ped. Surg. 7:546–52, 1972.
49. Fisher, J. F., DeLuca, F. G., and Swenson, O.: Rectal biopsy in Hirschsprung's disease, Z Kinderchir. 2:67, 1965.
50. Fraser, G. C., and Berry, Cl: Mortality in neonatal Hirschsprung's disease; with particular reference to enterocolitis, J. Pediat. Surg. 2:205, 1967.
51. Swenson, O.: A new surgical procedure in the treatment of Hirschsprung's disease, Surgery 28:371, 1950.
52. Swenson, O., Fisher, J. H., and Scott, J. E. S.: Diarrhea following rectosigmoidectomy for Hirschsprung's disease, Surgery 48:419, 1960.
53. Swenson, O.: Sphincterotomy in the treatment of Hirschsprung's disease, Ann. Surg. 160:540, 1964.
54. Grob, M.: Zur Technik der Rectosigmoidektomie bei Megacolon congenitum (Hirschsprung), Helvet, Chir. Acta 19:336, 1952.
55. Soave, F.: Hirschsprung's disease: Clinical evaluation and details of a personal technique, Z. Kinderchir., suppl.:66, 1966.
56. Duhamel, B.: Retrorectal and transanal pull-through procedure for the treatment of Hirschsprung's disease, Dis. Colon Rectum 7:455, 1964.

57. Duhamel, B.: A new operation for the treatment of Hirschsprung's disease, Arch. Dis. Child. 35:38, 1960 (a).
58. Duhamel, B.: Une nouvelle operation pour le megacolon congenital: l'abaissement retrorectal et trans-anal du colon, et son application possible au traitement de quelques autres malformations. Presse Med. 64:2249, 1956.
60. State, D.: Durgical treatment for idiopathic congenital megacolon (Hirschsprung's disease), Surg. Gynec. Obstet. 95:201, 1952.
61. Bowings, A. C. et al. The management of H.D. in the neonate. Aust. Ped. J. 8:121–7, 1972.
62. Susukie, H. et al.: Nonoperative diagnosis of H.D. in neonates. Pediatrics 51:188–91, 1973.
63. Nixon, H. H.: The present status of H. D., J. Med. Leban. 27 (4):401–5, 1974.2

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

Tumors of the Umbilicus

V. CHAROENKUL, M.D., A. DELCAMPO, M.D., A. DERBY, M.S., W. J. B. HODGSON, M.B., AND A. J. McELHINNEY, M.D.

Introduction

Tumors of the umbilicus are rare, although the first reported case of a metastatic umbilical nodule was given as long ago as 1847 (1), and it was not until 1864 that the first complete case study was reported by Storer (2). However, at St. Mary's Hospital in Rochester Minnesota, Sister Mary Joseph, the Superintendent, had noted that in many patients with intraabdominal cancer there was a firm nodule present in the umbilicus. During the time she frequently was the first assistant of Dr. William Mayo, who founded the Mayo Clinic, she brought this to his attention and although the information was freely circulated orally, it was never at that time published. Sir Hamilton Bailey suggested that the nodule should be given the name Sister Joseph's Nodule in her honor and also to commemorate that era of medicine (3).

Sister Joseph's Nodules, which are defined as a malignant lesion, and exclude endometriosis, are rare; out of a grand total of 260 cases reported in the world literature, there have only been three reports in the American medical literature (4, 5, 6) in the last 8 years. Two cases with metastatic umbilical tumors have recently been seen at this hospital and their management is discussed. A review of the records of the Bronx Veterans Administration Hospital and The Mount Sinai Hospital over the past ten years yielded no additional cases.

Case Reports

Case 1. A 63-year-old black man had adenocarcinoma of the splenic flexure of the colon and underwent left hemicolectomy. At operation, liver metastases were noted. Three months later, he had a firm mass 2 × 3 cm situated in the umbilicus (Fig. 1). A biopsy of the lesion revealed metastatic adenocarcinoma. A course of radiotherapy resulted in some regression in the tumor mass but the patient died three months later. At autopsy, generalized metastatic disease was noted in the abdominal cavity extending directly through the abdominal wall into the umbilicus.

Case 2. A 61-year-old white man was admitted with a three-month history of pain in the epigastrium and back, weight loss of 20 lbs. and a firm tender umbilical nodule 2.5 × 2 cm (Fig. 2). A cytologic study of a specimen obtained by scraping the umbilical tumor was only able to suggest an adenocarcinoma. The site of the primary tumor was not revealed with an upper GI series, barium enema, IVP, liver scan, liver biopsy and bone survey, all of which were normal. The patient underwent an exploratory laparotomy and was found to have a carcinoma of the body of the pancreas with multiple peritoneal metastases involving the umbilicus. Because of the discomfort to the patient, the umbilicus was excised. Four weeks later, he died.

From the Department of Surgery, Bronx Veterans Administration Hospital, 130 W. Kingsbridge Road, Bronx, N. Y. 10468; and Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Dr. V. Charoenkul, Bronx V.A. Hospital, 130 W. Kingsbridge Road, Bronx, N.Y. 10468.

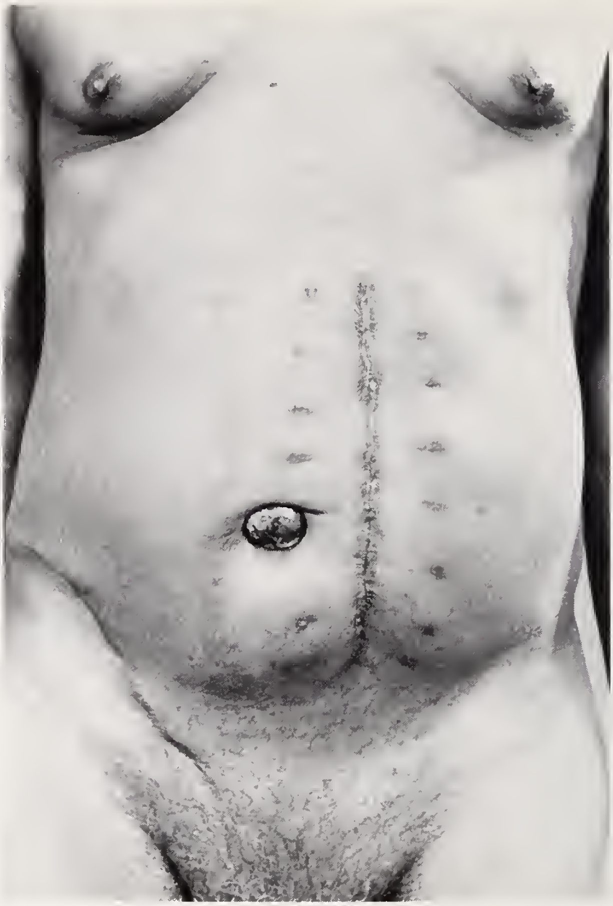

FIG. 1. Secondary umbilical tumor from the colon in case 1.

Discussion

In a summary of a review of the literature, Barrow (7) looked at 202 cases of umbilical tumors and found only a 8% incidence of primary malignant tumor. On the other hand, nearly 30% of cases were of unknown origin. When we reviewed the literature from 1966 to 1976, we found a further 58 cases of metastatic lesions to the umbilicus (4, 5, 6, 8–14) and when these cases were put together with Barrow's, and our two cases included, the incidence of unknown origin of umbilical tumor remained unchanged (Table I).

It is surprising that metastatic deposits do not occur more often in the umbilicus because superficial and deep lymphatics communicate with and may carry tumor to and from superficial axillary, deep axillary, inguinal, deep femoral, and periaortic lymph nodes. There may be communication from the bladder via the urachus. Venous communications may carry tumors via the lateral thoracic veins, the internal mammary veins, and the portal system. In addition to these anatomical features, direct extension of tumor

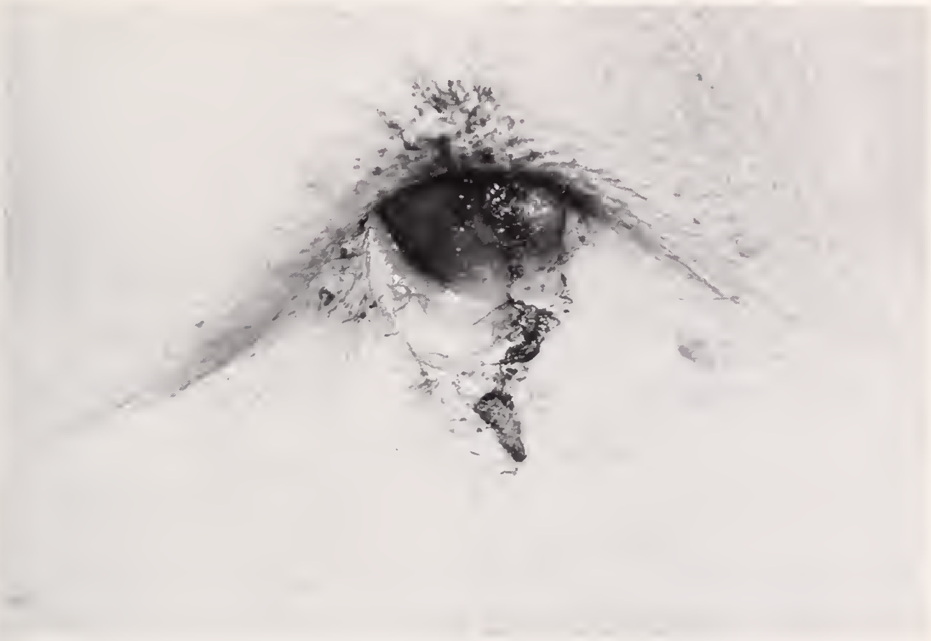

FIG. 2. Secondary umbilical tumor from the pancreas in case 2.

from the anterior peritoneal surface may occur and tumor emboli may lodge in the umbilicus via the arterial system. In our two cases, it is evident that direct extension of tumor occurred from the anterior peritoneal surface. It is clear that the presence of metastatic umbilical tumor suggests that the disease is in its late stages. However, life expectancy of up to three years has been reported in cases of metastatic carcinoma of the umbilicus (8) as well as in the primary lesions (15).

It is noteworthy that even a case following malignancy in the reticuloendothelial system has been described. This case had malignant ascites secondary to multiple myeloma (4). Even so, the stomach remains the commonest site from which the tumor metastasizes to the umbilicus but our two cases were in the comparatively less common sites of colon and pancreas.

When primary tumors of the umbilicus are reviewed (Table II) it would appear that the majority are in fact adenocarcinomas and these account for over half the cases reported (7, 9, 15–18). But, the diagnosis of primary adenocarcinoma must always be looked at with care as there must be many instances where it is difficult to distinguish a primary adenocarcinoma of the umbilicus from a secondary adenocarcinomatous deposit from elsewhere.

The diagnosis of tumors of the umbilicus is straightforward since macroscopically the lesion often completely replaces the umbilicus and is usually irregularly nodular or exfoliative. However, Flynn and Spurrett warn that in its early stages an umbilical tumor may be confused with endometriosis or an umbilical granuloma or have minimal changes so that it may easily be missed (12).

TABLE I

Metastatic Tumors of the Umbilicus (262 Cases)

Site	M. V. B. (7)	R. R. (9)	B. D. (10)	V. T. F. B. R. S. (12)	V. A. This Paper	K. T. et al (13)	I. Z. A. S. (6)	A. B. (8)	K. L. (14)	A. C. (11)	M. G. C. R. C. N. Jr. (5)	H. B. S. I. L. (4)	Total	Percent
Unknown	59	16	3										78	29.9
Stomach	50	1	9	1				1		1			63	24.0
Ovary	25	4	3	1									33	12.6
Colon & Rectum	20	1	4		1	1	1						28	10.3
Pancreas	15				1								16	6.1
Biliary Tract	7	1	1			1							10	3.8
Uterus	6	2											8	3.1
Liver	5												5	1.9
Endometrium	3									1			4	1.5
Sarcoma	3												3	1.5
Small Bowel	2												2	0.8
Fallopian Tube	1										1		2	0.8
Cervix	1	1											2	0.8
Breast	1	1											2	0.8
Kidney	1	1											2	0.8
Appendix	1												1	0.4
Penis	1												1	0.4
Prostate	1												1	0.4
Reticulo-Endothelial												1	1	0.4

TABLE II

Primary Tumors of the Umbilicus

Site	M. V. B. (7)	M. D. (17)	B. A. et al (15)	P. R. L. (16)	R. R. (9)	G. G. (18)	Total	Percent
Adenocarcinoma	29	1	1	1		1	33	53.2
Sarcoma	13	1					14	22.6
Melanoma	10				1		11	17.7
Squamous Cell Carcinoma	2						2	3.2
Basal Cell Carcinoma	2						2	3.2

We only have experience in the management of metastatic tumors of the umbilicus and it would appear from our cases that the aggressive approach of operating to remove the metastatic deposit, which has been advocated (16, 18), is unsuccessful. We obtained much better results in the case that was given radiotherapy, and this also has its advocates (7, 15). We would advise that radiotherapy is always given in cases of metastatic tumors of the umbilicus because of the very poor outlook of the patient at presentation. This would be particularly true if the patient's primary lesion is in a solid organ, but it is recognized that if the primary tumor is in a hollow viscus then operative intervention may be required to prevent or relieve obstruction. However, excision of the umbilicus is of dubious benefit to the patient.

Conclusion

Two patients at the Bronx Veterans Administration Hospital had Sister Joseph's Nodules and although this is a rare condition, a review of the world literature and a review of the management of these two cases would suggest that radiotherapy is the treatment of choice when such nodules are seen since they usually represent late stages of carcinomatous disease. However, it would be rewarding to inspect the umbilicus closely in all patients as it is possible that in early stages secondary tumors of the umbilicus may be missed.

Acknowledgment

The authors gratefully acknowledge the editorial assistance of Dr. F. Giron.

References

1. Cullen, T. S.: *Embryology, Anatomy and Diseases of the Umbilicus.* Saunders, Philadelphia, 1916, pp. 118–458.
2. Storer, H. R.: Cases Illustrative of Obstetric Disease. Case V, Boston Med Surg J 70:69, 1864.
3. Bailey, H.: *Demonstration of Physical Signs in Clinical Surgery,* 13th Edition. Williams and Wilkins, Baltimore, 1970, p. 356.
4. Bank, H. and Liberman, S. I.: Sister Joseph's Nodule and Malignant Ascites in Multiple Myeloma, New Engl J Med 284:676, 1971.
5. Couturier, M. G. and Neale, R. C., Jr.: Adenocarcinoma of Umbilicus Secondary to Fallopian Tube Carcinoma, Amer J Obstet Gynec 105:32, 1969.

6. Zeligman, I. and Schwilm, A.: Umbilical Metastasis from Carcinoma of the Colon, Arch Dermatol 110:911, 1974.
7. Barrow, M. V.: Metastatic Tumors of the Umbilicus, J Chron Dis 19:1113, 1966.
8. Brodetti, A.: Umbilical Metastases from Cancer of the Stomach, Rassegna Int Clin Terap 47:684, 1967.
9. Ramsch, R.: Benign and Malignant Umbilical Tumors, Bruns Beitr Klin Chir 215:461, 1967.
10. Duperrat, B.: Umbilical Metastases—A Propos of Twenty Personal Specimens, Bull Soc Franc Derm Symph 75:638, 1968.
11. Colantuono, A.: Metastases to the Umbilicus Revealing Cancer of the Stomach, Ross Int Clin Ter 49:429, 1969.
12. Flynn, V. T. and Spurrett, B. R.: Sister Joseph's Nodule, Med J Austral 5:728, 1969.
13. Tsushima, K., Yamagata, N., Mikami, T., and Sasamura, M.: Metastatic Carcinoma of the Umbilicus, Iryo 24:416, 1970.
14. Lauslahti, K.: Malignant External Endometriosis, Acta Path Microbiol Scand 233:98, 1972.
15. Alvisi, B., Musconi, B., and Spodoni, G.: Umbilical Adenocarcinoma, Cancro 23:23, 1970.
16. Lalatta, P. R.: Adenocarcinoma of the Urachus in an Umbilical Site, Arch Ital Chir 92:900, 1966.
17. DiFilippo, M.: Study of Two Cases of Adenoma and Reticulosarcoma of the Umbilicus, Arch De Vecchi Anat Path 51:991, 1967.
18. Glazer, G.: Primary Adenocarcinoma Arising in a Vitello-Intestinal Duct Remnant at the Umbilicus, Brit J Surg 60:247-249, 1973.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, Mach-April, 1977
Printed in U.S.A.

The Coexistence of Asymmetric Septal Hypertrophy, Rheumatic Mitral Valve Disease, and Infectious Endocarditis: A Case Report

GREGORY R. D'ONOFRIO, JR., M.D., HAROLD Z. SCHEINMAN, M.D., JAMES T. MAZZARA, M.D., AND PATRICK J. McKENNA, M.D.

The association of asymmetric septal hypertrophy with variable left ventricular outflow tract obstruction and mitral insufficiency is well documented. Bacterial endocarditis is rarely reported as a complication of this cardiomyopathy; however, coexistent rheumatic valvulitis has never been reported. We are reporting the case of a man with asymmetric septal hypertrophy, bacterial endocarditis and rheumatic valvulitis documented at necropsy.

Case Report

A 56-year-old man was transferred from another institution to St. Vincent's Hospital and Medical Center of New York in October, 1973 for cardiac catheterization. A heart murmur had been discovered in 1969 without a history of rheumatic fever. He was in his usual state of good health until June, 1973 when he developed progressive dyspnea, anorexia, weight loss, and weakness. He was admitted to the referring institution two months after the onset of symptoms where a diagnosis of subacute bacterial endocarditis was made after Streptococcus viridans was cultured from the blood. The initial impression was rheumatic heart disease and mitral insufficiency. He was treated with 20 million units of penicillin intravenously per day. Congestive heart failure which developed responded poorly to digitalization and furosemide.

On examination the patient appeared as a chronically ill-looking man in mild respiratory distress. The blood pressure was 100/60 mm Hg and the pulse was 80/minute and regular. Rales were audible over both posterior lung fields. The jugular venous pulse was elevated at 45 degree elevation. Peripheral arterial pulses were equal throughout with a brisk upstroke. A heaving apical impulse was palpable in the left anterior axillary line. A systolic thrill was palpable at the apex. On auscultation the rhythm was regular. The second heart sound was physiologically split with accentuation of the pulmonic component. The first sound was diminished in intensity. A grade 5/6 even frequency holosystolic murmur heard maximally at the lower left sternal border radiated toward the apex and the left axilla. A third sound was audible, but no opening snap, ejection sounds, or systolic clicks were heard.

Chest x-ray showed left ventricular enlargement and pulmonary venous congestion. Sinus rhythm and left ventricular hypertrophy were evident on the electrocardiogram. Echocardiography was not available at the time.

Cardiac catheterization (Table I) demonstrated severe pulmonary hypertension and a resting intraventricular gradient of 88 mm Hg. There was no change in brachial artery pulse pressure following ventricular premature contractions (Fig. 1). There was no calcification either of the aortic or mitral valves and no aortic or mitral valve gradients were found. A left ventriculogram performed in the right anterior oblique projection demonstrated 4+ mitral

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From the Department of Medicine, Section of Cardiology, St. Vincent's Hospital and Medical Center of New York.

Supported in part by United States Public Health Service and National Heart and Lung Institute Grant #3 T01 HL 05686-09S1.

Requests for reprints should be sent to: Harold Z. Scheinman, M.D., Director of Laboratories, Long Beach Memorial Hospital, Long Beach, N.Y. 11561.

TABLE I

Catheterization Data

Pressures S/D (mean)	
Right atrium (mmHg)	(11)
Right ventricle (mmHg)	79/11
Pulmonary artery (mmHg)	79/38 (57)
Pulmonary capillary wedge (mmHg)	(30) V = 50
*Left ventricle (mmHg)	178/32
*Left brachial artery (mmHg)	90/54 (74)
Mean outflow tract gradient (mmHg)	63
Peak outflow tract gradient (mmHg)	88
Pulmonary vascular resistance (dynes-sec-cm^{-5})	701
Systemic vascular resistance (dynes-sec-cm^{-5})	1896
Cardiac output (L/min)	3.08
Cardiac index (L/min/m^2)	2.08
Arteriovenous oxygen difference (ml/100ml)	5.74

* Simultaneous equisensitized

regurgitation and a subvalvular chamber. Surgery was recommended but postponed because of the patient's debilitated condition. On the 35th hospital day he developed atrial fibrillation with a rapid ventricular response. Despite supportive measures for progressive left ventricular failure, he expired on the thirty-ninth hospital day.

At post mortem examination the heart was enlarged and weighed 500 grams (Fig. 2). There was considerable thickening of the left ventricular wall and septum. The septum measured 27 mm in the subaortic valvular region. The left ventricular free wall behind and inferior to the posterior mitral leaflet was thickened and rounded. It progressively decreased in thickness from base to apex. The postero-basal left ventricular free wall thickness was 17 mm. The septal- to free-wall ratio was 1.6. The mural endocardium of the left ventricular outflow tract was moderately thickened and the ventricular cavity was reduced in volume.

Microscopic examination of the septal myocardium revealed a bizarre arrangement of bundles of muscle fibers coursing in various directions and separated by connective tissue and clefts (Fig. 3). Higher magnification of this septal area revealed the cardiac fibers to be hypertrophic, bizarrely shaped, and disorganized. Sample of the left ventricular free wall revealed hypertrophic muscle fibers with normal shape and orientation.

The mitral valve leaflets were thickened, deformed and retracted; the chordae tendineae were thickened and shortened, consistent with chronic rheumatic valvulitis. The anterior leaflet of the mitral valve revealed a 1.5 cm perforation. The endocardium of the left atrium above the posterior mitral leaflet showed an area of roughness and thickening consistent with a McCallum's patch. Microscopic examination of the heart failed to reveal any active rheumatic process, i.e., Aschoff bodies. Other significant findings were mural thrombi in the right atrial appendage, pulmonary emboli with bilateral lower lobe infarction and a liver consistent with passive congestion.

Discussion

In 1957 Brock (1) demonstrated asymmetric hypertrophy of the left ventricle with systolic outflow obstruction. During the last 17 years the clinical entity of asymmetric septal hypertrophy (ASH) has been clarified, elucidated and categorized in terms of a spectrum of subgroups, pathophysiology and clinical course (2–4). Most investigators (5) believe that ASH falls into the category of an obstructive cardiomyopathy.

The disease is usually first evident with the discovery of a heart murmur with subsequent development of dyspnea, effort syncope, and angina. It may

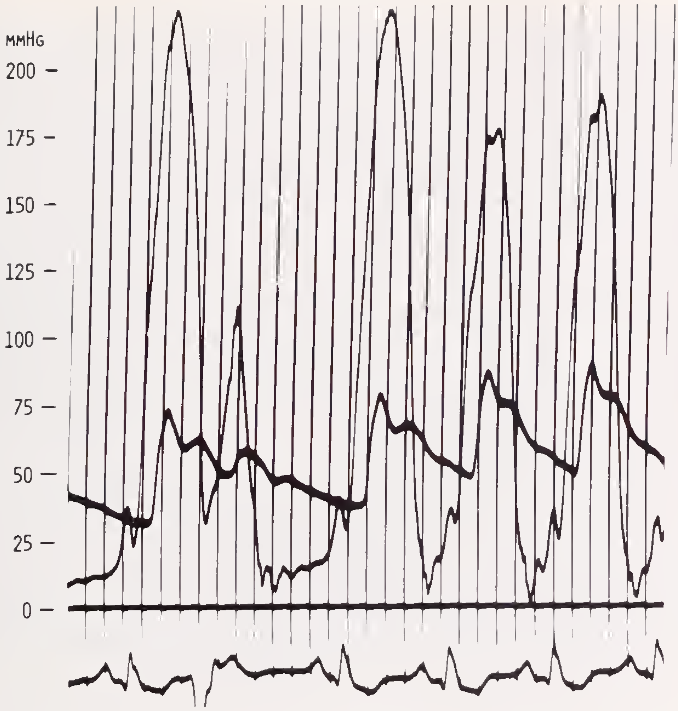


FIG. 1. Simultaneous equisensitive recording of left brachial artery and intraventricular pressure demonstrating typical configuration of arterial tracing with normal upstroke, an intraventricular systolic pressure gradient and no change in pulse pressure following a ventricular premature contraction (Time line interval 0.04 sec).

follow a benign course or a rapid downhill course with progressive symptoms. Sudden death may occur in the absence of outflow tract obstruction.

Epstein et al (4) further delineated this spectrum of subgroups and emphasized the existence of a common unique morphologic alteration of asymmetric septal hypertrophy. This entity is transmitted as an autosomal dominant trait. Nonobstructive and obstructive symptomatic and asymptomatic subgroups have been identified. Maron and coworkers and Henry et al (6, 7) have further demonstrated differences in distribution of myocardial abnormalities in each of these groups of patients. Patients with symptomatic nonobstructive asymmetric septal hypertrophy have a disarray of myofibrils of the septum and left ventricular free wall. Patients with obstructive asymmetric septal hypertrophy have these changes localized to the ventricular septum. These differences are discernable by gross light and electron microscopic examination as well as by echocardiography.

Boiteau and Allenstein (8) first reported a case of idiopathic hypertrophic subaortic stenosis (IHSS) and bacterial endocarditis. Since that time the association has been made only rarely, and in our survey of the literature we found only eighteen cases of IHSS and bacterial endocarditis (9–15). Because of this association, prophylactic antibiotics have been recommended.

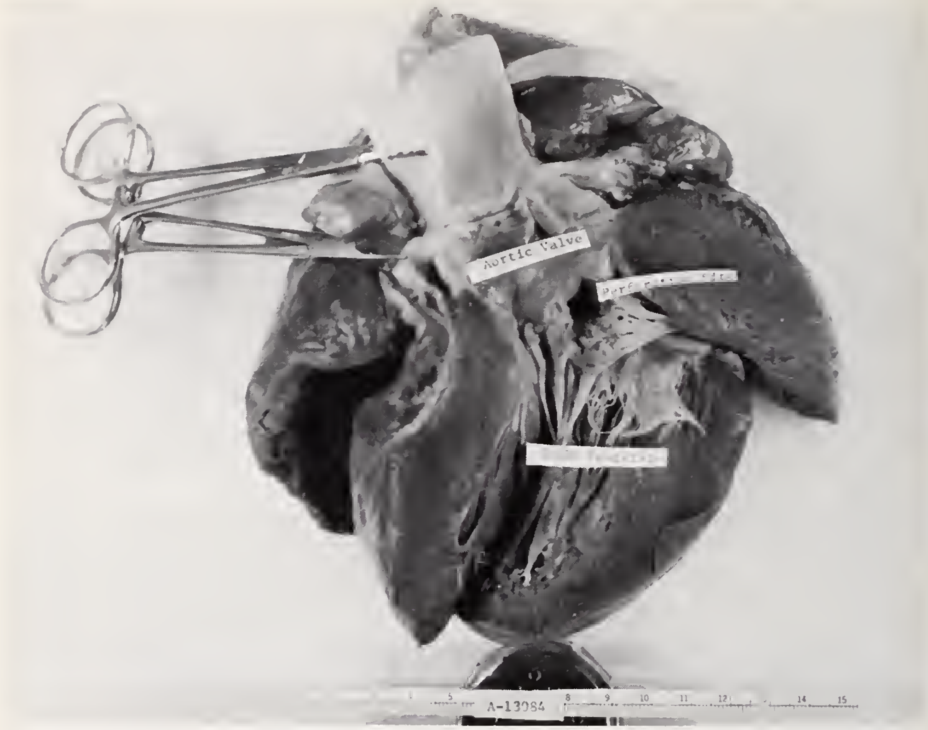


FIG. 2. The heart is enlarged and reveals considerable asymmetric hypertrophy of the septum. There is a recent perforation of the anterior leaflet of the mitral valve.

Frank and Braunwald (16) estimated the incidence of bacterial endocarditis and IHSS at 2.3% after study of 126 patients with hemodynamically documented IHSS followed over a 12-year period. There were 3 cases of definite bacterial endocarditis and an additional 3 patients who had febrile illness suspicious of endocarditis and responding to antibiotics. The lesions of endocarditis may occur either on the subaortic area distal to maximum obstruction or on the deformed incompetent mitral valve.

The patient we have presented entered the hospital with acute severe mitral insufficiency. He had no previous history of rheumatic fever. Hypertrophic subaortic stenosis was considered in the precatheterization evaluation. At the time of the procedure a systolic gradient of 88 mm Hg was demonstrated across the outflow tract with no gradient across the aortic valve. The left ventriculogram showed 4+ mitral regurgitation, no mitral valve calcification, hypertrophied left ventricle with fair contractility and a subvalvular chamber. Extrasystoles induced during the left heart catheterization showed no change in the brachial artery pulse pressure. At catheterization the findings of a dynamic subvalvular outflow tract gradient, lack of calcification of the aortic valve, rapid brachial artery upstroke and lack of postextrasystolic rise of brachial artery pulse pressure was consistent with

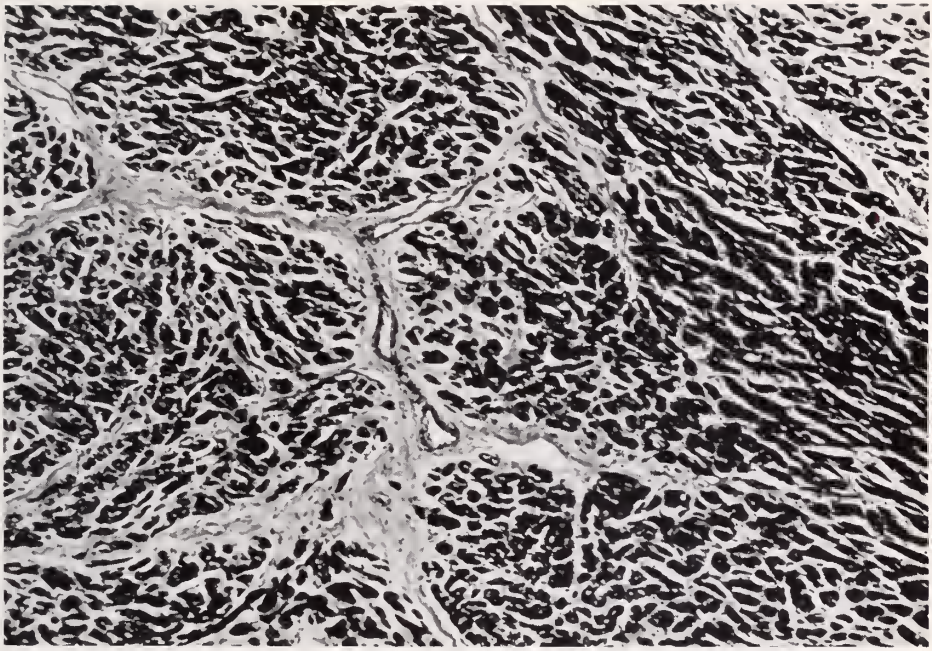


FIG. 3. Histologic section of ventricular septal myocardium demonstrating disarray of myofibrils. The individual fibers are hypertrophic, bizarrely shaped, and course in various directions (Hematoxylin and Eosin ×10).

obstructive asymmetric septal hypertrophy. The mitral insufficiency was thought to be either a manifestation of hypertrophic subaortic stenosis or a result of ruptured chordae tendinae subsequent to endocarditis. We did not consider rheumatic mitral disease a likely possibility.

Necropsy demonstrated a perforation of the anterior mitral leaflet due to endocarditis and stigmata of chronic rheumatic valvulitis.

Summary

A 56-year-old man had treated bacterial endocarditis, congestive heart failure and severe mitral regurgitation. Cardiac catheterization documented obstructive asymmetric septal hypertrophy and mitral regurgitation. The patient expired despite efforts to control progressive left ventricular failure. Autopsy revealed evidence of asymmetric septal hypertrophy, rheumatic valvulitis and perforation of the mitral valve leaflet secondary to endocarditis. The coexistence of these findings has not been previously reported in our review of the literature.

Acknowledgment

The authors thank Dr. Charlotte Dolecki, Department of Medicine, St. Vincent's Hospital and Medical Center of New York, who referred the patient for cardiovascular evaluation. Thanks are also due to the photographer, Mr. Rudolph Hennings.

References

1. Brock, R.: Functional Obstruction of the Left Ventricle, Guy's Hosp Rep 106:221, 1957.
2. Clark, C. E., Henry, W. L., and Epstein, S. E.: Familial Prevalence and Genetic Transmission of Idiopathic Hypertrophic Subaortic Stenosis, N Engl J Med 289:709, 1973.
3. Henry, W. L., Clark, C. E., and Epstein, S. E.: Asymmetric Septal Hypertrophy (ASH). The Unifying Link in the IHSS Disease Spectrum, Circulation 47:827, 1973.
4. Epstein, S. E., Henry, W. L., Clark, C. E. et al: Asymmetric Septal Hypertrophy, Ann Intern Med 81:650, 1974.
5. Goodwin, J. F., and Oakley, C. M.: The Cardiomyopathies, Br Heart J 34:545, 1972.
6. Maron, B. J., Ferrans, V. J., Henry, W. L. et al: Difference in Distribution of Myocardial Abnormalities in Patients with Obstructive and Non-Obstructive Asymmetric Septal Hypertrophy (ASH): Light and Electron Microscopic Findings, Circulation 50:436, 1974.
7. Henry, W. L., Clark, C. E., Roberts, W. C. et al: Differences in Distribution of Myocardial Abnormalities in Patients with Obstructive and Non-Obstructive Asymmetric Septal Hypertrophy (ASH): Echocardiographic and Gross Anatomic Findings, Circulation 50:447, 1974.
8. Boiteau, G. M. and Allenstein, B. J.: Hypertrophic Subaortic Stenosis. Clinical and Hemodynamic Studies with Special Reference to Pulse Contour Measurement, Am J Cardiol 8:614, 1961.
9. Linhart, J. W. and Taylor, W. J.: Bacterial Endocarditis in a Patient with Idiopathic Hypertrophic Subaortic Stenosis, Circulation 34:595, 1966.
10. Nagle, J. P.: Idiopathic Hypertrophic Subaortic Stenosis and Bacterial Endocarditis, JAMA 200:643, 1967.
11. Vecht, R. J., Oakley, C. M.: Infection Endocarditis in Three Patients with Hypertrophic Obstructive Cardiomyopathy, Br Med J 2:455, 1968.
12. Epstein, E. and Coulshed, N.: Bacterial Endocarditis in Idiopathic Hypertrophic Subaortic Stenosis, Cardiologia (Bosch) 54:30, 1969.
13. Cardelia, J. U., Befeler, B., and Hildner, F. J.: Hypertrophic Subaortic Stenosis Complicated by Aortic Insufficiency and Subacute Bacterial Endocarditis, Am Heart J 81:543, 1971.
14. Chretien, J. H., Limos, C., and Garagusi, V. F.: Association of Bacterial Endocarditis with Idiopathic Hypertrophic Subaortic Stenosis, South Med J 66:269, 1973.
15. Wang, K., Gobel, F. L., and Gleason, D. F.: Bacterial Endocarditis in Idiopathic Hypertrophic Subaortic Stenosis, Am Heart J 89:359, 1975.
16. Frank, S., and Braunwald, E.: Idiopathic Hypertrophic Subaortic Stenosis: Clinical Analysis of 126 Patients with Emphasis on the Natural History, Circulation 37: 759, 1968.

THE MOUNT SINAI JOURNAL OF
MEDICINE
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

A Nonsurgical Approach to the Treatment of Upper Gastrointestinal Hemorrhage: A Preliminary Report

JOSEPH MORMINO M.D., FRANCIS TAFT, AND SAMUEL R. POWERS M.D.

ABSTRACT

The effects of aramine solution, locally instilled at the site of upper gastrointestinal hemorrhage through a nasogastric tube, were evaluated.

The initial experiments were conducted on dogs. Gastric blood flow studies were performed in these animals to determine whether the effect of the aramine solution was systemic or topical.

Subsequent double-blind studies were performed on 17 humans with upper gastrointestinal bleeding. Nasogastric lavage either with saline or aramine solution was employed. Excellent results were obtained in the control of gastric and duodenal bleeding. Systemic toxicity of aramine was minimal. The aramine effect appeared to be local rather than systemic.

The control of upper gastrointestinal hemorrhage continues to be a major therapeutic problem.

Gastric cooling (1, 2, 3), iced saline lavage, and systemic vasopressor agents have produced variable results in the control of bleeding (4, 5, 6). A better approach to this problem may be the use of a vasoconstrictor drug with selective action on the gut, or the administration of an agent with a direct topical effect on the site of hemorrhage. In this study the effects of a locally applied drug are investigated.

Aramine (metaramine bitartrate), is a vasoconstricting agent initially developed for systemic application. However, it functions as a potent vasoconstrictor when applied locally over exposed small vessel endings. It has been selected for use in these experiments over other vasoconstricting agents because of its longer duration of action. Studies employing isotopically labeled aramine show that it is taken up by the granular structures in the sympathetic nerve endings, replacing norepinephrine (7).

Animal Studies

Experimentation was initially performed on German shepherd dogs with an average weight of 35 Kg. The animals were anesthetized with nembutal intravenously (30mg/K). Laparotomy was performed and the stomach opened. Multiple lacerations were then made on the entire mucosal surface of the posterior wall of the stomach. 25 cc of solution (control and experimental) were instilled over the bleeding gastric mucosa at one-half hour intervals, and then aspirated from the open stomach for determination of the hemato-

From the Departments of Surgery, Albany Medical Center, Albany, N. Y. 12208; and The Mount Sinai Medical Center, New York, N. Y. 10029

Requests for reprints should be sent to: Joseph Mormino, M.D., 11 Ralph Pl., Suite 308, Staten Island, N. Y. 10304.

crit and hemoglobin concentrations. The procedure was done in a double-blind manner employing normal saline as the control and aramine solution (300mg/liter normal saline) as the experimental agent. A total of 30 determinations was performed.

The effects of these solutions on gastric blood flow were determined by the radioactive Xenon-133 clearance technique similar to that employed by Selkurt (8) for the determination of blood flow in the intestines. Blood flow was determined by introducing radioactive Xenon-133 (0.3–.6 microcuries) into the celiac artery through a catheter which had been passed retrograde after insertion into the femoral artery. Each determination of blood flow in both the control and aramine studies was obtained after the test solution had been introduced into the stomach by a nasogastric tube. Blood flow was determined by the process of tail subtraction employing the Kety formula (8):

$$F = \frac{0.693\lambda}{T_{\frac{1}{2}}\rho}$$

Where λ is the absorption coefficient of Xenon, T is the halftime and ρ is the specific weight of the stomach, which is assumed to be proportional to 1.

In all experiments on animals, constant monitoring of venous and arterial pressures as well as pulse rate and respirations was carried out.

In order to evaluate the validity of the use of the hematocrit and hemoglobin present in the gastric aspirate as an estimate of the rate of hemorrhage, the following procedure was performed. A nasogastric tube was passed through the esophagus into the stomach of an anesthetized dog. Serial quantities of the animals blood were injected directly through the stomach wall after a laparotomy had been performed. In each experimental determination the quantity of blood ranged from 10cc to 50cc. 25cc of saline was injected into the nasogastric tube after each quantity of blood was injected. The solution was then aspirated and a hematocrit and hemoglobin was determined on each sample. The results obtained are graphically represented in Figures 1 and 2. These results indicate the use of hematocrit and hemoglobin concentration in the aspirate is a valid method to determine the rate of hemorrhage in the stomach.

Clinical Studies

Subsequent studies were performed on human subjects with upper gastrointestinal hemorrhage. A total of 17 studies (7 control, 10 aramine) was conducted. The site and etiology of the hemorrhage was determined by various methods including upper GI series, endoscopy and in several instances by subsequent surgery. Documentation of the site and etiology was obtained in 13 of the 17 patients. Experiments were conducted in a double-blind manner employing normal saline as the control and aramine solution (300mg/liter normal saline) as the test agent. Six determinations were performed in each study. 250cc of either solution was instilled into the stomach via a nasogastric tube. This solution was allowed to remain in the stomach for 30 minutes and was then aspirated. A sample of the aspirate was analyzed for

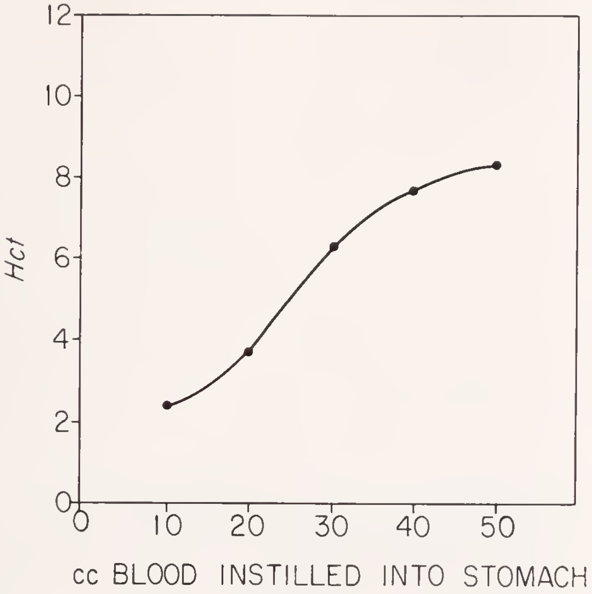


Fig. 1.

hematocrit and hemoglobin. Each patient's vital signs were monitored every 5 minutes.

Results and Discussion

There was a significant difference in the hematocrit and hemoglobin value of the gastric aspirate in the control and aramine treated dogs. In all the animals, hemorrhage was either stopped or significantly decreased following the instillation of aramine solution. The hemorrhage was not halted immediately, however, a minimum of two to three instillations of aramine solution was necessary in order to lessen or stop bleeding.

In the control group, there was no significant change in the rate of hemorrhage throughout the entire series of experimental determinations. At no time was there any change in vital signs and venous pressure either in the control or aramine groups.

Radioactive Xenon-133 blood flow studies revealed that there was no significant change in the rate of blood flow through the stomach in either control or experimental.

Three-compartment blood flow rate (total blood flow in the stomach is composed of three compartments: mucosa, rapid flow; musculature, intermediate flow; and connective and supportive tissue, slow flow) remained constant both for control and aramine groups.

Results obtained in human subjects with gastrointestinal bleeding were similar to those obtained in dogs. The rate of hemorrhage in the seven patients of the control group was not significantly changed by instillation of

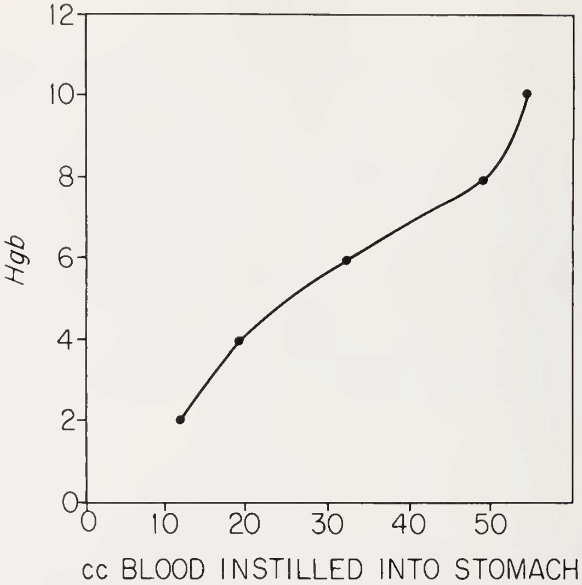


FIG. 2.

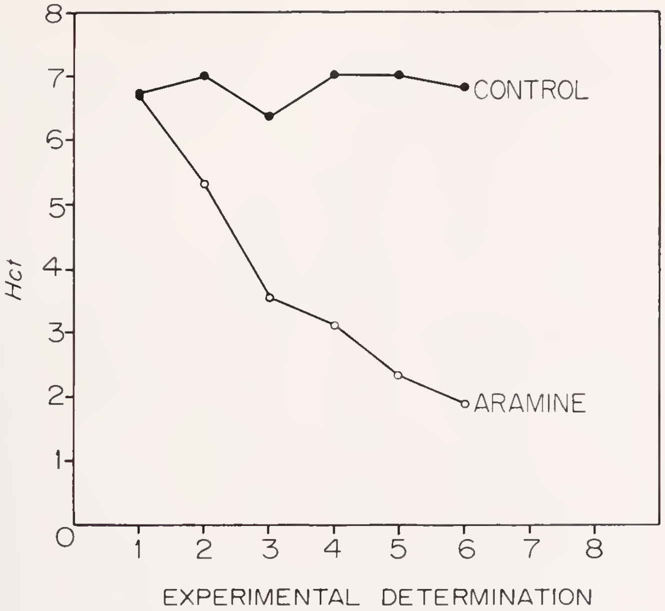
normal saline solution into the stomach. All patients subsequently underwent gastric surgery at a later date.

Data obtained from patients treated with aramine solution show this agent to be effective in the treatment of gastric and duodenal hemorrhage. The mean rate of hemorrhage was decreased to approximately one-fourth of its initial rate (Figs. 3, 4). Seven of ten patients were noted to have a slight pink discoloration of the aspirate at the end of the sixth and final determination. Hematocrit and hemoglobin concentrations were too low to be calculated in most cases.

Case Report

#11 N.W., a 35-year-old man was admitted to Albany Medical Center, Albany, New York, because of hematemesis on several occasions that day. The patient had had two previous gastrointestinal bleeding episodes over a four-year period. Endoscopic examination on the day of admission revealed the site of hemorrhage to be an ulcer on the anterior surface of the duodenum. Multiple attempts to control the hemorrhage with iced saline lavage were unsuccessful. The patient was then placed in the study group. Aramine solution was employed on a double-blind basis. The aspirate from the third and subsequent determinations were shown to have no detectable hematocrit or hemoglobin. There was no further bleeding following the aramine therapy. An elective pyloroplasty was performed at a later date.

Comparison of final hemoglobin determinations between control and aramine groups both in human and animal revealed a t-statistic = 3.374. At .01 confidenc level critical t-statistic limits are: −2.624, t 2.624 for 14 degrees of freedom. Therefore, the values are statistically significant in difference.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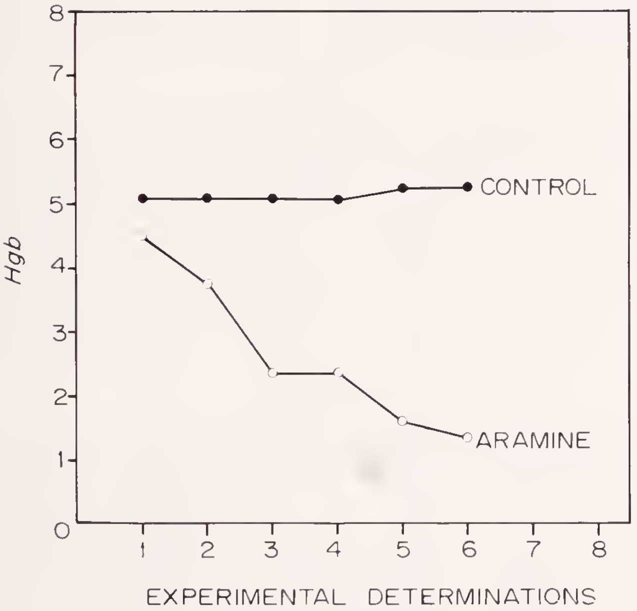
CONTROL
ARAMINE
EXPERIMENTAL DETERMINATION

Fig. 3.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CONTROL
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EXPERIMENTAL DETERMINATIONS

Fig. 4.

Comparison of final hematocrit determinations between control and aramine groups in both humans and animals revealed a t-statistic = 2.799. At .01 confidence level critical t-statistic limits are −2.624, t −2.624 for 14 degrees of freedom. Therefore, the difference between the two groups is significant statistically.

In all cases where the aramine solution was effective, its response was noted to begin after approximately one hour.

There was no improvement in only one human in the aramine study group. The patient was initially hemorrhaging at a rapid rate and continued to hemorrhage, throughout the entire series of experimental determinations. Other forms of medical therapy were attempted but none was successful. At surgery a duodenal ulcer with a large open artery was observed.

On one occasion there was recurrence of hemorrhage six hours after cessation of aramine therapy. A second course of treatment quickly halted the bleeding. There was no subsequent bleeding.

Complications were noted in only one aramine treated patient. The patient had had a pyloroplasty several years prior to admission. It was noted that we were unable to aspirate most of the aramine solution following its instillation into the stomach. After the third trial, an increase in blood pressure and pulse rate was noted. The patient became diaphoretic and atrial flutter developed. Therepy was halted immediately. Symptoms persisted for approximately one hour after which the vital signs returned to normal and the flutter disappeared (Table II).

Of the 17 studies performed, diagnosis of the underlying etiology was made

TABLE I

Control Group

Cases	Determinations					
	1st	2nd	3rd	4th	5th	6th
1 HCT	3.0	4.0	2.0	3.7	3.0	2.4
1 HGB	2.2	2.6	2.0	2.6	2.2	2.0
2 HCT	4.1	4.0	4.2	5.0	4.0	4.4
2 HGB	3.2	3.9	4.0	3.7	3.2	3.9
3 HCT	6.0	4.5	4.5	4.9	4.8	5.4
3 HGB	5.5	4.0	4.4	3.5	4.0	4.3
4 HCT	9.1	9.0	8.6	8.8	10.3	10.0
4 HGB	7.0	6.8	7.0	7.3	8.0	8.0
5 HCT	4.5	6.0	5.5	5.8	4.5	5.0
5 HGB	4.0	4.2	3.8	4.2	4.3	4.3
6 HCT	7.2	7.2	7.0	7.0	8.5	8.0
6 HGB	6.0	5.8	5.5	6.0	6.8	6.1
7 HCT	12.4	13.0	13.5	13.5	14.0	13.4
7 HGB	8.1	8.4	9.0	8.6	8.5	8.6
Mean HCT	6.6	6.8	6.4	7.0	7.0	6.9
Mean HGB	5.1	5.1	5.1	5.1	5.3	5.3
SD:HCT	3.3	3.3	3.8	3.3	4.0	3.8
HGB	2.1	2.0	2.3	2.2	2.5	2.4

Hemoglobin and hematocrit of gastric aspirate

TABLE II

Aramine Group

Cases	Determinations					
	1st	2nd	3rd	4th	5th	6th
8 HCT	7.2	6.1	5.7	*	*	*
8 HGB	6.5	5.5	4.8	*	*	*
9 HCT	6.5	4.0	1.0	0.7	1.0	1.0
9 HGB	4.0	2.3	1.0	1.0	1.0	1.0
10 HCT	7.5	6.7	5.0	6.0	4.9	2.0
10 HGB	6.2	5.8	4.0	5.8	3.2	2.2
11 HCT	7.0	6.5	5.0	4.0	1.5	1.0
11 HGB	4.5	4.5	3.0	2.9	1.5	1.1
12 HCT	6.0	2.5	0.0	0.0	0.0	0.0
12 HGB	3.1	1.0	0.0	0.0	0.0	0.0
13 HCT	5.1	4.9	3.6	2.8	1.1	1.0
13 HGB	4.0	4.0	2.7	2.0	0.6	0.6
14 HCT	4.1	3.0	1.9	1.5	1.2	1.0
14 HGB	3.3	2.8	1.6	1.0	1.0	1.1
15 HCT	5.2	5.1	3.0	1.9	0.0	0.0
15 HGB	4.6	4.7	2.8	1.3	0.0	0.0
16 HCT	13.0	12.0	11.6	11.0	11.0	10.9
16 HGB	7.0	7.1	6.8	7.3	7.1	7.0
17 HCT	6.3	2.9	0.0	0.0	0.0	0.0
17 HGB	3.5	1.5	0.0	0.0	0.0	0.0
Mean HCT	6.7	5.3	3.5	3.1	2.3	1.9
Mean HGB	4.5	3.7	2.4	2.4	1.6	1.4
SD:HCT	2.6	3.0	3.6	3.5	3.6	3.4
HGB	1.3	2.0	2.1	2.6	2.3	2.2

in 13. Seven patients were noted to be hemorrhaging from gastric or duodenal ulcers. Six were observed to be bleeding from gastritis. In the other four cases, the exact etiology remained undetermined. There was no significant statistical difference between those patients who had bled from ulcers and those who had bled from gastritis. The aramine solution appeared to be equally effective in both instances with the exception of the previously cited patient with a large artery in the base of a duodenal ulcer.

Conclusions

Aramine is a vasoconstricting agent initially developed for systemic application. However, it functions as a potent vasoconstrictor when applied locally over exposed small vessel endings.

It can be deduced from these experiments that aramine acts to decrease vessel diameter primarily by a selective action on the vessels which are exposed at the site of hemorrhage. This deduction is based on the observation that blood flow was not altered during the aramine experiments on dogs. In other words, the ability of aramine to stop gastrointestinal hemorrhage is neither through a systemic effect nor through local absorption but by a selective effect on the exposed vessel endings.

Although aramine is known to be absorbed by the small intestines, it can be used with relative safety. However, we advocate extreme caution when using this drug in patients with rapid gastric emptying.

We believe that the topical application of aramine is an effective nonsurgical method in the treatment of upper gastrointestinal hemorrhage.

Acknowledgment

We are grateful to Mr. Alfred Cote, Mr. Warren Creel, and Mr. Mark English for their technologic aid, as well as to Miss Rosemarie Mormino.

References

1. Holt, M. H.: A Simple Cooling Device for Treatment of Upper Gastrointestinal Bleeding, **Surgery** 50:728, 1961.
2. Nicoloff, D. M., Griffen, W. O., Salmon, P. A., Peter, E. T., and Wangensteen, O. H.: Local Gastric Hypothermia in the Managements of Massive Gastrointestinal Hemorrhage. **Surg Gynec Obstet** 144:495 1962.
3. Wangensteen, S. L., Orahood, R. C., Voorhees, A. B., Smith R. B., and Healey, W. V.: Intragastric Cooling in the Management of Hemorrhage from the Upper Gastrointestinal Tract, **Am J Surg** 105:401, 1963.
4. Baum, S., Nusbaum M., and Tumen H. R.: The Control of Gastrointestinal Hemorrhage by Selective Mesenteric Arterial Infusion of Pitressin, **Gastroenterology** 58:926, 1970.
5. Crystal Raymond F.: Vasopressin in the Treatment of Hemorrhagic Gastritis, Amer **Surgeon** 34:895, 1968.
6. Rosch J., Gray R. K., Grollman J. H., Ross G., Steckel R. J., and Weiner M.: Selective Arterial Drug Infusion in the Treatment of Acute Gastrointestinal Bleeding, **Gastroenterology** 59:341, 1970.
7. Goodman, L. S. and Gilman, A.: The Pharmacological Basis of Therapeutics, 4th Edition: 508, 1970.
8. Selkurt, E. E., Wathen, R. L.: Washout of Intra-Arterially Injected Xenon-133 from the Intestines of the Dog as a Method for Estimating Blood Flow, **Gastroenterology** 52:388, 1967.

THE MOUNT SINAI JOURNAL OF
MEDICINE
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

MEDICOLEGAL NOTES

MICHAEL G. MACDONALD, J. D. AND KATHRYN C. MEYER, J. D., COEDITORS

Availability of Privileges at Private Hospitals

The availability of privileges at private voluntary (i.e., nonprofit) hospitals to community physicians has traditionally been a source of dissension between physicians and hospital governing boards. To the practicing physician, privileges at a prestigious voluntary hospital permit him to provide his patients with a range of services not available at a community hospital and give status to his practice. Hospital governing boards, faced with growing legal responsibility for the performance of their medical staffs, are concerned with maintaining standards of quality, as well as avoiding overcrowding of facilities and preserving the prestige of the institution. Teaching hospitals in addition need to preserve affiliation relationships with medical schools.

The right of governing boards to establish criteria for staff membership was at one time unquestioned. The courts consistently held that a voluntary hospital had absolute discretion to impose whatever requirments for membership it saw fit. Although courts from time to time made references to a possible exception for the hospital which had "monopoly power," as a practical matter governing board decisions were rarely if ever set aside.

However, beginning with the civil rights movement in the 1950s, there has been a growing intrusion of the legal concept of due process into many areas of the private sector which were once sacrosanct. A variety of groups have pressed for the view that private institutions must be held to the same standards of reasonableness and fairness in their activities as are public institutions. These appeals have often found receptive audiences in the courts, which have increasingly brought the private sector to the bar of public scrutiny. In New York, however, it was not the courts but the legislature that changed the situation as to privileges with the enactment of §2801-b of the Public Health Law in 1972. This provision made it an improper practice for a hospital to exclude a physician, podiatrist, or dentist from staff membership "without stating the reasons therefore, or if the reasons stated are unrelated to standards of patient care, patient welfare, the objectives of the institution or the character or competency of the applicant." Persons claiming to be aggrieved by such improper practice were given the right to appeal to the public health council. The statute authorized the council to investigate, and if it found the complaint justified, to direct the hospital to review its decision.

The courts still had a role, however, since the enactment of this statute left New York hospitals and physicians with two unanswered questions: (1) to what extent would "teeth" be put in the requirement by making hospital

From the Legal Department, The Mount Sinai Medical Center, New York, N.Y. 10029.

action subject to review in the courts, and (2) would "objectives of the institution" be interpreted broadly enough to include such objectives as maintaining standards of excellence, avoiding overutilization, or maintaining teaching affiliations.

At least a partial answer was received in the decision last April of the New York's highest court, the Court of Appeals, in *Fritz v. Huntington Hospital.* Two osteopaths were denied privileges at Huntington Hospital, a private voluntary hospital, because they failed to submit evidence of completion of American Medical Association approved training programs. The physicians had both graduated from Colleges of Osteopathy, had both completed accredited, although not AMA-approved, internship programs, were both licensed to practice medicine in the State of New York, and had each been practicing for approximately 12 years. Although they had privileges at another area hospital, 85% of their patients resided in the area served by Huntington Hospital. Pursuant to §2801-b, they appealed the Hospital's decision to the Public Health Council. The Council found that it was "inappropriate [for the Hospital] to demand an AMA-approved internship and/or residency in instances in which Doctors of Osteopathy are applying for hospital privileges" and concluded that the Hospital had violated §2801-b. When the Hospital continued to deny the physicians privileges, they brought a legal action that eventually found its way to the Court of Appeals and became the first case to be decided under the new statute.

The first question before the Court was whether the statute gives the courts authority to review the action of a private hospital. Here the court's answer was clear. Although in the past private hospitals had sole discretion to exclude physicians, now judicial review and enforcement would be available for decisions by the public health council. Indeed, requests for review could be made by the aggrieved physicians themselves, not just the council.

The court then turned to the question of which reasons for denying privileges would be legally acceptable. The court noted that Huntington Hospital had introduced no evidence that AMA-approved programs were better than the internship program completed by the two physicians. Although hospitals were free to be selective and need not accept every licensed applicant, the decision of the Hospital in this case had not been based on the actual medical credentials and capabilities of the applicants, which had been found to be adequate by the State examining boards, and the two doctors should therefore be granted privileges. The court concluded its opinion with the following warning:

> The availability of health services is a matter of vital public concern and hospitals, which are charged by statute with the obligation of providing high quality, efficient and effective services at a reasonable cost, should direct their best efforts toward ameliorating medical services shortages and increasing the availability of physicians, especially to persons in the community in which they serve.

Thus, while the court refused to prohibit hospitals from establishing requirements that go beyond the licensing laws, the thrust of the opinion indicated that it would scrutinize such requirements carefully to ensure that they in fact measure professional competence. The extent to which the court would recognize the validity of requirements which relate to institutional needs, rather than physician ability, remained undecided.

Until further judicial interpretations are available, hospitals would be advised to review their membership criteria carefully and to make certain (1) such criteria relate to the character or competency of the applicant, standards of patient care or the objectives of the institution, (2) such criteria are clearly stated in the medical staff bylaws, and (3) procedures are devised to assure that such criteria are evenly and fairly applied. Absent this type of approach, a private institution, no longer able to rely on the shield that it is private, may find its actions with respect to privileges subject to legal scrutiny.

The Mount Sinai Journal of Medicine
Vol. 44, No. 2, March–April, 1977
Printed in U.S.A.

RADIOLOGIC NOTES*

CLAUDE BLOCH, M.D. and HARVEY M. PECK, M.D., Coeditors

Case No. 392

Submitted By

MING T. CHUANG, M.D., ALVIN S. TEIRSTEIN, M.D., and
BERNARD B. ROBINSON, M.D.

A 72-year-old white male smoker and New York City resident, whose employment took him to Italy and Israel, was admitted to the hospital with a cough productive of small amounts of red blood. Physical examination revealed only dullness to percussion in the left inferior axillary region. Routine laboratory data, barium enema, and intravenous pyelogram were normal. Posterioanterior and left anterior oblique views of the chest (Figs. 1 A and 1B) revealed a 6.0 × 7.5 centimeter mass in the left lower lobe abutting on the pleura, but causing no peural reaction. The lesion was sharply demarcated and contained no calcification or cavitation. There was no peripheral atelectasis. The contours of the mass were lobulated and the remainder of the lung fields was normal.

Discussion

The dog is the definite host of the tapeworm Echinococcus granulosa, with a variety of mammals serving as intermediate hosts, particularly sheep and man (1, 2). The pastoral variety of E. granulosa is common in the sheep raising areas of the Mediterranean, Africa, New Zealand and Australia. A sylvatic form of the disease has been reported in Alaska and Canada (3). Ova of the small tapeworm are passed from the small intestine of the dog and are ingested by grazing sheep, and occasionally by man. The larvae develop in the duodenum of the intermediate host. Upon entering the blood stream, most of the larvae are filtered out in the liver and lung, while a few may reach the bones, kidneys, brain and spleen. The vast majority of larvae cause no disease. After a latent period of up to 20 years, the few surviving larvae become manifest as pulmonary or liver cysts and may cause cough and hemoptysis (4). Orienta et al (5) reported 301 patients with pulmonary hydatid cysts. Cough occurred in 59% and hemoptysis in 41%. The Casoni skin test was positive in 70% of the patients and eosinophilia of greater than 8% occurred in 22%. 242 of the 301 patients had a solitary cyst on chest roentgenogram. Lower lobe cysts were the most common; thirty-five percent occurring in the right lower lobe and 22% in the left lower lobe. The cysts had attained 6–8 cm in size when first detected.

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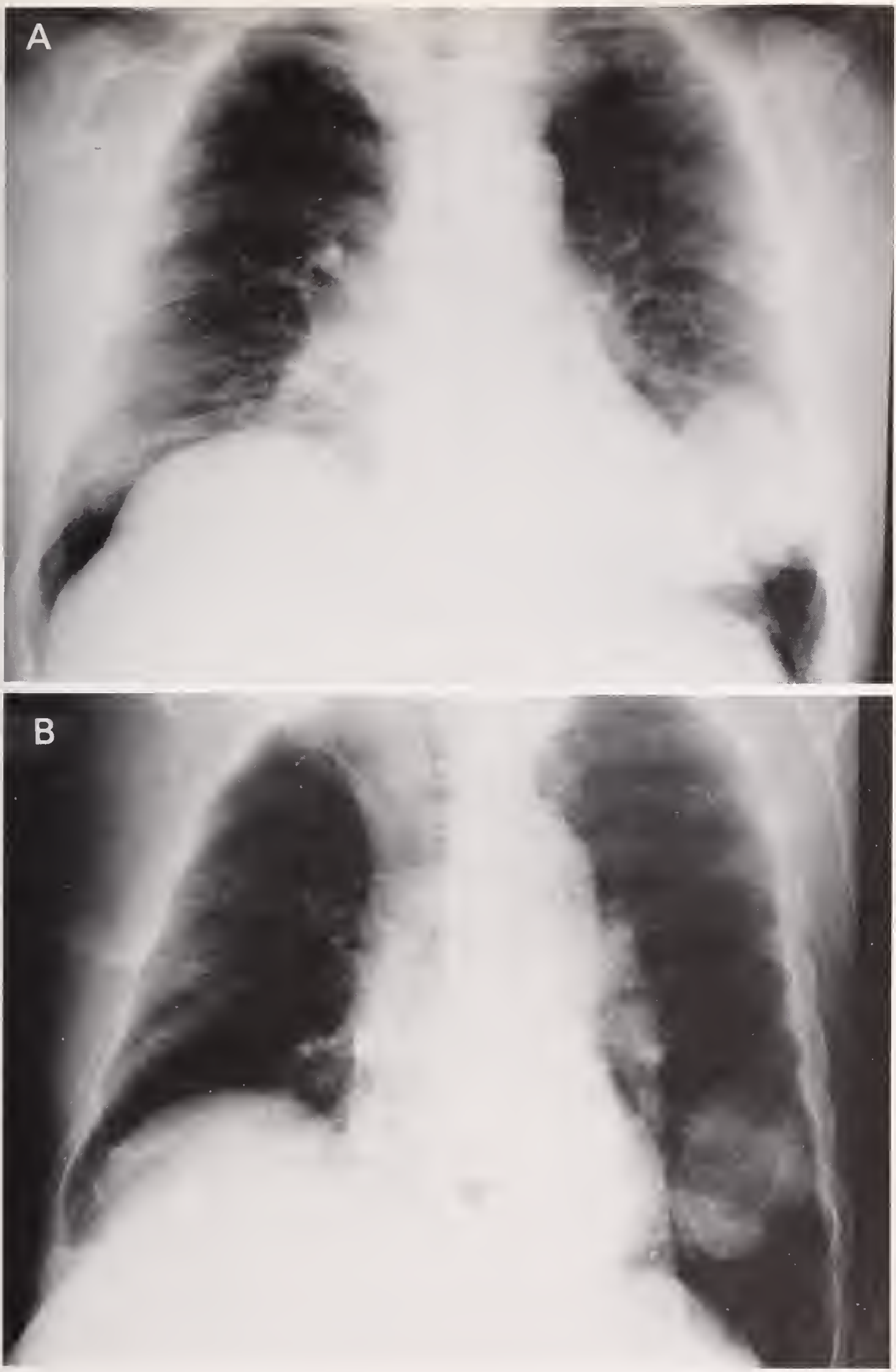
* From the Department of Radiology, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.



Case 392, Fig. 1A. There is a 6.0 × 7.5 centimeter, smoothly marginated lobulated mass in the left lower lobe abutting on the pleura, but causing no pleural reaction. There are no cavities or calcifications within the lesions, and there is no evidence of peripheral atelectasis.

Case 392, Fig. 1B. The lobulated contour of the mass is better appreciated in the left anterior oblique projection.

In the lung, the Roentgen differential diagnosis includes primary and metastatic carcinomas and other pulmonary cysts. When the cysts rupture into a bronchus, an air-fluid level may become visible and must be differentiated from a lung abscess. Occasionally, air may enter between the two layers of the cyst, (exocyst and endocyst) giving rise to a crescent of air around the cyst, the "meniscus sign" (6), which may be confused with a mycetoma (7, 8).

A pulmonary hydatid cyst should be considered in any patient with a large, sharply circumscribed pulmonary mass who lived or traveled in an area where E. granulosa is endemic. Treatment of choice is lobectomy. Bronchoscopy is absolutely contraindicated for fear of rupturing the cyst.

Case Report: Ecchinococcal cyst of the lung.

References

1. McPhail, J. L. and Arora, T. S.: Intrathoracic Hydrated Disease, Dis Chest 52:772–781:1967.
2. Cifarelli, F. P.: Radiological Diagnosis of Hydatidosis, Acta Radiol Interna 5:17–27:1955.
3. Katz, A. M. and Pan, C. T.: Echinococcus Disease in the United States, Amer J Med 25:759–770:1958.
4. Chrysospathis, P.: Echinococcus Cysts of the Lung, Dis Chest 49:278–283:1966.
5. Bloomfield, J. A.: Protean Radiological Manifestations of Hydrated Infestations, Australasian Radiol 10:330–343:1966.
6. Schlanger, P. M. and Schlanger, H.: Hydatid Disease and Its Roentgen Picture, Amer J Roentgen 60:331–347:1948.
7. Weens, H. S. and Thompson, E. A.: The Pulmonary Air Meniscus, Radiology 54:700–705:1950.
8. Goldberg, B.: Radiologic Appearances in Pulmonary Aspergillosis, Clin Radiol 13:106–114:1962.
9. Orueta, A. F., Montero, A., Prieto, J. and Durarte, G.: Surgical Treatment of Hydatid Cysts of the Lung, Br J Dis Chest 68:183–192:1974.

Case No. 393

*Submitted by**

JEFFREY S. FREED, M.D. and ARTHUR SICULAR, M.D.

The patient came to the hospital with signs, symptoms and laboratory data consistent with acute cholecystitis and choledocholithiasis. The symptoms and signs of fever, right upper quadrant pain, tenderness, and guarding were associated with serum bilirubin of 3.8 mgm percent, serum alkaline phosphatase of 150 units (normal 40–80 units), and an intravenous cholangiogram revealing a dilated bile duct (14 mm in diameter), as well as two radiolucencies within the ducts; contrast medium was seen to enter the duodenum. Two weeks prior to admission, the patient had an upper gastrointestinal series for dyspeptic symptoms. The study revealed two medium sized duodenal diverticula, multiple jejunal diverticula, but no other significant abnormalities (Fig. 1). With conservative management, the patient's acute episode improved on antibiotics and intravenous fluids. Because of persistent pain and tenderness, the patient underwent exploratory laparotomy. Findings at the time of surgery included a chronically contracted gall bladder with multiple calculi, and a dilated common duct with palpable stones. The gall bladder was removed in a retrograde manner and the common duct was opened, with modifications occasioned by a previous aortic graft placement, and a previous right transverse colostomy. A one-centimeter stone was easily removed with stone forceps. Dilators and forceps passed into the distal duct encountered resistance to intraduodenal passage, repeatedly obtaining grumous calculous material. With a transverse duodenotomy, and a Bakes #4 dilator in the common duct, the papilla of Vater could not be identified. After repeated passages, it was noted that there were three duodenal passages, afferent and efferent duodenum, and a mouth of a long diverticulum (at least 6 cm) on the posteromedial wall of the second portion of the duodenum, at the apex of which the Bakes dilator tip could be palpated. With this identifying feature, all the calculous gravel could be removed from the ampulla, and the dilator passed through the diverticulum into the main channel of the duodenum. A standard closure of the duodenum was accomplished, and the common duct was repaired over a #14 F T-tube.

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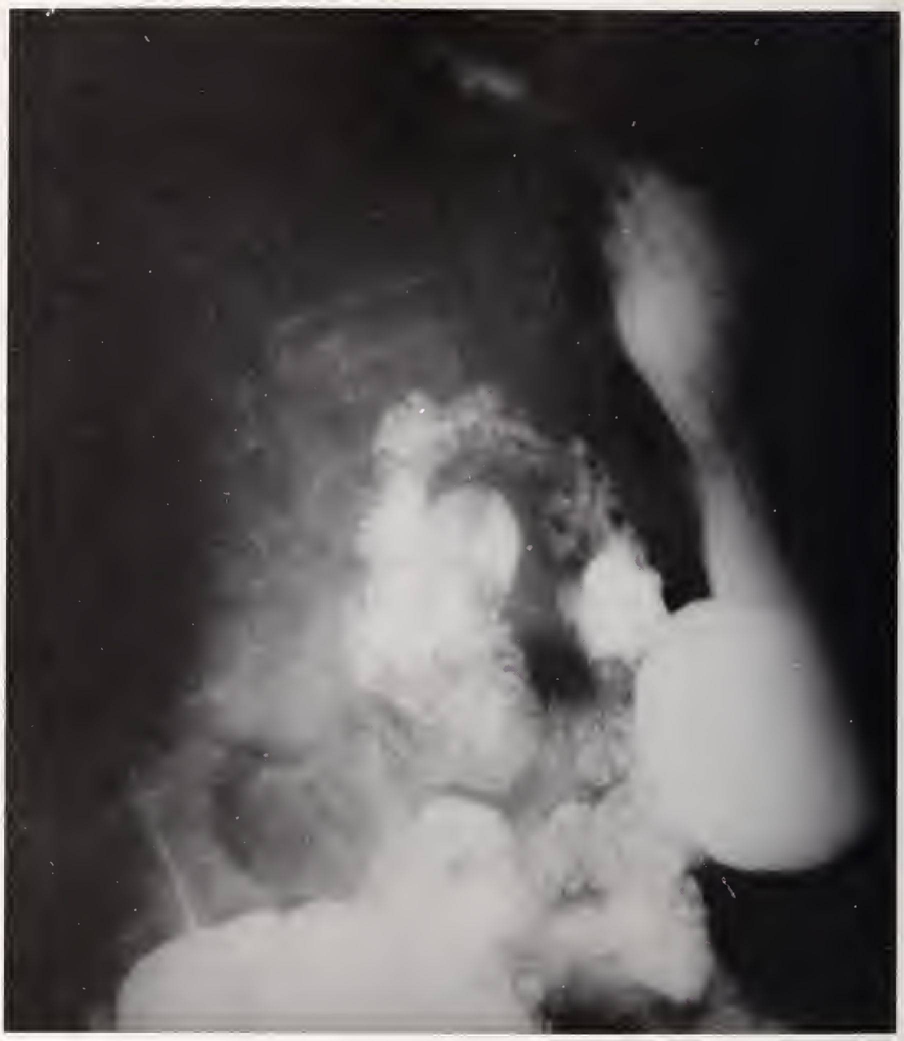
* From the Department of Surgery, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

After an uneventful course, a T-tube cholangiogram and GI series done simultaneously on the tenth post-operative day revealed a normal appearing, slightly dilated common duct without residual stones, with free flow of contrast material into the diverticulum and duodenum, with visualization of the main pancreatic duct as a common channel (Fig. 2).

Discussion

The purpose of this report is to emphasize the significance of the "incidental" finding of a duodenal diverticulum in a patient with choledocholithiasis. Simple choledochoduodenotomy and -ostomy would have left the patient with residual obstruction of the main pancreatic duct despite the free flow of bile into the bypass. The unusual anatomy (common duct terminating in the papilla of Vater within the diverticulum) makes a duct exploration very difficult, enhancing the chance of creating false passages or duodenal perforation, and incomplete removal of calculi. In this instance, the surgeon must be aware of the anatomic possibilities, and be prepared for the difficult decision of formal duodenotomy to handle the common bile duct exploration.

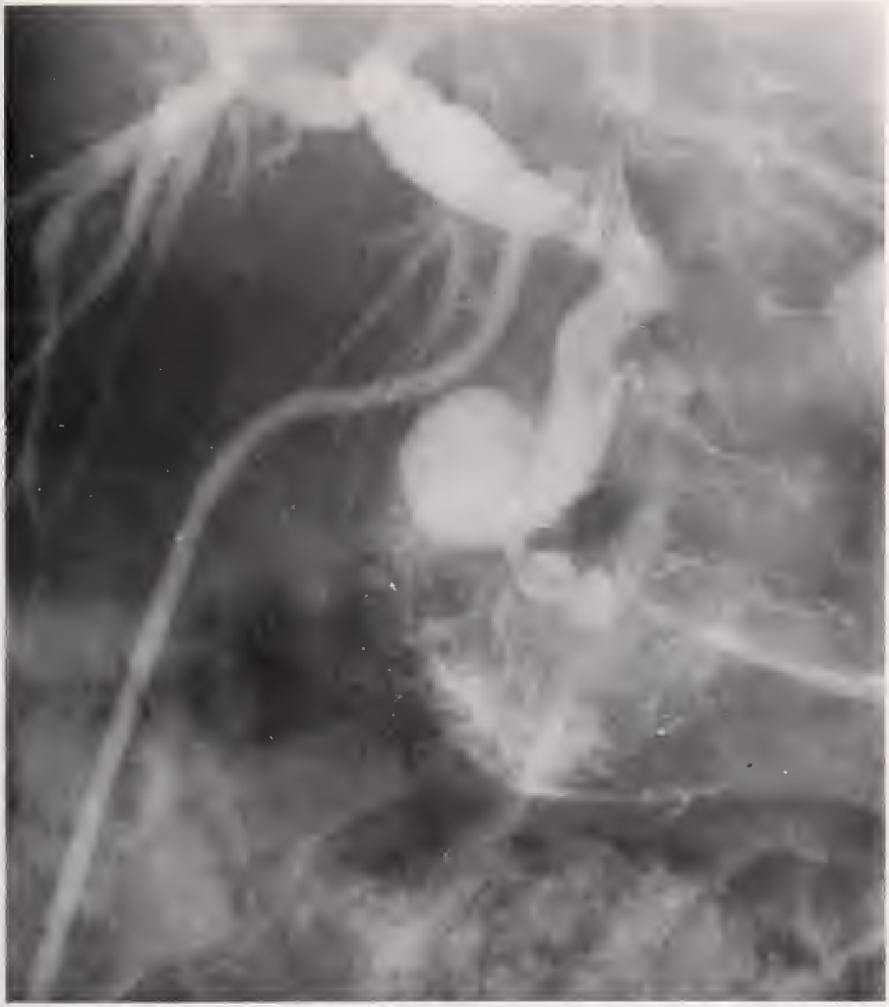
The case also is an illustration of potential catastrophe that might accompany the ill-advised duodenal diverticulectomy for incompletely evaluated symptoms. A preoperative upper gastrointestinal series is an essential part of every common duct exploration. Cholangiography combined with hypotonic



Case 393, Fig. 1. Upper gastrointestinal series in the right anterior oblique projection reveals a rounded, large perivaterian diverticulum with a broad neck. A smaller diverticulum is also noted within the fourth portion of the duodenum.

duodenography may be used to better demonstrate the fine details of the duodenal diverticular anatomy (8, 9).

Duodenal diverticula are an incidental finding on upper gastrointestinal series in a reported incidence of between .01 and 5 percent (1) and in autopsy series between 3 and 15 percent (2). The removal of asymptomatic or incidentally encountered diverticula is not recommended. This judgment stems from the fact that statistically few patients harboring the anatomic abnormality suffer any sequelae from their presence. Dependent diverticula of the third



Case 393, Fig. 2. T-tube cholangiogram reveals a slightly dilated biliary system with a few residual calculi. A common channel is identified with filling of a portion of the main pancreatic duct. The duodenal diverticulum fills directly at the ampulla of Vater.

portion of the duodenum however may cause stasis and relate to malnutrition or the blind loop syndrome.

There are reported cases of acute duodenal diverticulitis (2), hemmorrhage proven by selective arteriography (7), and necrosis of the diverticular wall secondary to obstruction of the neck of the diverticulum (3). Pressure upon the pancreatic ducts has led to acute pancreatitis (4), and compression of the common bile duct has led to obstructive jaundice (5). Diverticular hemmorrhage has led to the discovery of resectible tumors within the diverticula (6).

Case Report: ANOMALOUS BILIARY AND PANCREATIC DUCT INSERTION INTO DUODENAL DIVERTICULA

References

1. Jones, T. W. and Merendino, K. A.: The Perplexing Duodenal Diverticulum, Surgery 48:1068, 1960.
2. Zeifer, H. D. and Goersch, H.: Duodenal Diverticulitis with Perforation, Arch Surg 82:746, 1961.
3. Munnell, E. R. and Preston, W. J.: Complications of Duodenal Diverticula, Arch Surg 92:152, 1966.
4. Maclean, N. J.: Duodenal Diverticulitis, Ann Surg 85:73, 1927.
5. Hadley, F. H.: Biliary Obstruction: A Case of Common Bile Duct Obstruction as a Complication of Duodenal Diverticulum, J Kansas Med Soc 63:51, 1962.
6. Sheldon, W. C.: Gastrointestinal Hemmorrhage from Duodenal Diverticula, Am J Dig Dis 4:817, 1959.
7. Miller, R. E., McCabe, R. E., Salomon, P. F., and Know, W. G.: Surgical Complications of Small Bowel Diverticula Exclusive of Meckel's, Ann Surg 171:202, 1970.
8. Willox, G. L. and Costopoulos, L. B.: Entry of Common Bile and Pancreatic Ducts into a Duodenal Diverticulum, Arch Surg 98:447, 1969.
9. Nelson, J. A., and Burhenne, J. H.: Anomalous Biliary and Pancreatic Duct Insertion into Duodenal Diverticula, Radiology 120:49, 1976.

Case No. 394

*Submitted by**

MYRON MELAMED, M.D.

A 33-year-old man was admitted with a left-sided abdominal mass of one year's duration and progressively increasing abdominal pain. Physical examination revealed a poorly defined mass in the left lumbar zone. Urinalysis showed no abnormal findings. Liver-spleen scan was normal.

Intravenous pyelogram (Fig. 1) demonstrated a large mass on the left side of the abdomen with contralateral displacement of the left renal collecting system. The stomach and small bowel were also displaced to the right and the splenic flexure was depressed by the mass (Fig. 2). Aortography (Fig. 3) revealed marked displacement of the abdominal aorta and its branches. The left renal artery was displaced to the right paralumbar area and selective left renal arteriography (Fig. 4) showed marked deformity of the left kidney bordering a large avascular mass.

At surgery, a huge left renal cyst was found containing 3,000 cc of clear, amber fluid. The cyst was incised along its base and the line of excision in the renal cortex was oversewn. Then the kidney was replaced to the left side, in its normal fossa.

Selected tomogram (Fig. 5) from an intravenous pyelogram eight months later reveals the left kidney to be normal in position with relatively minimal deformity of the collecting system.

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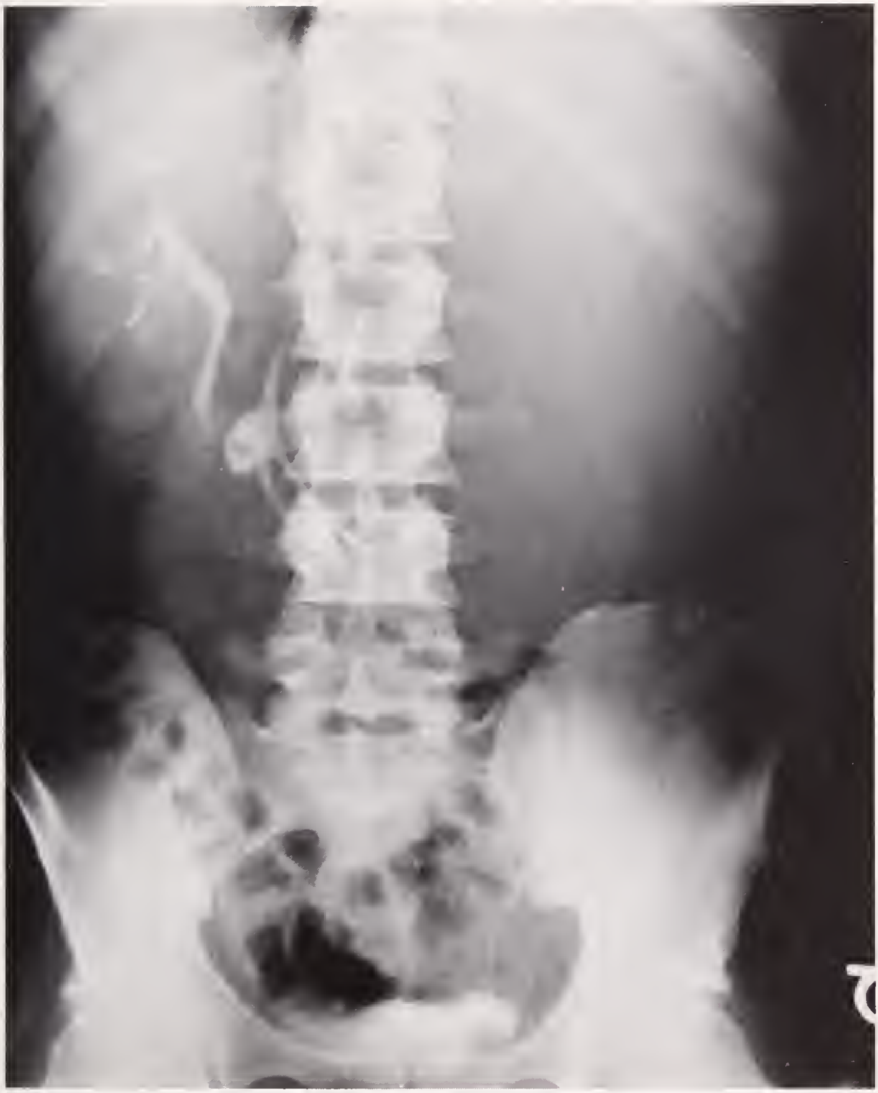
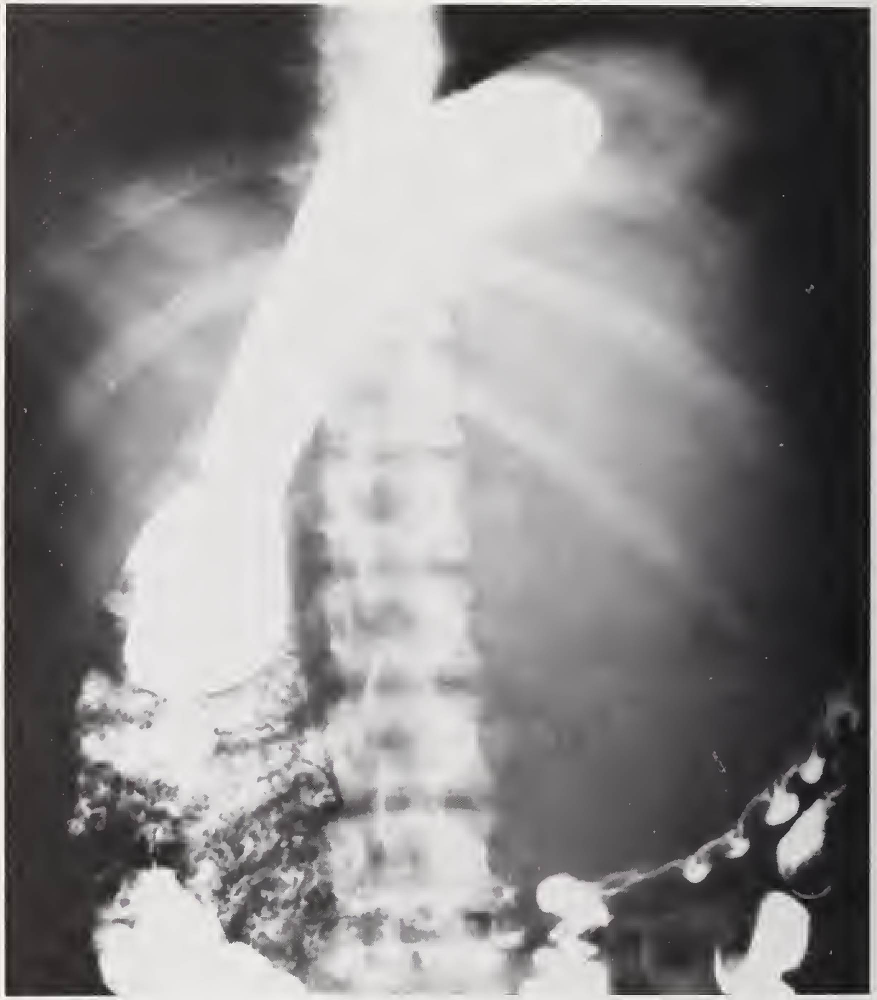
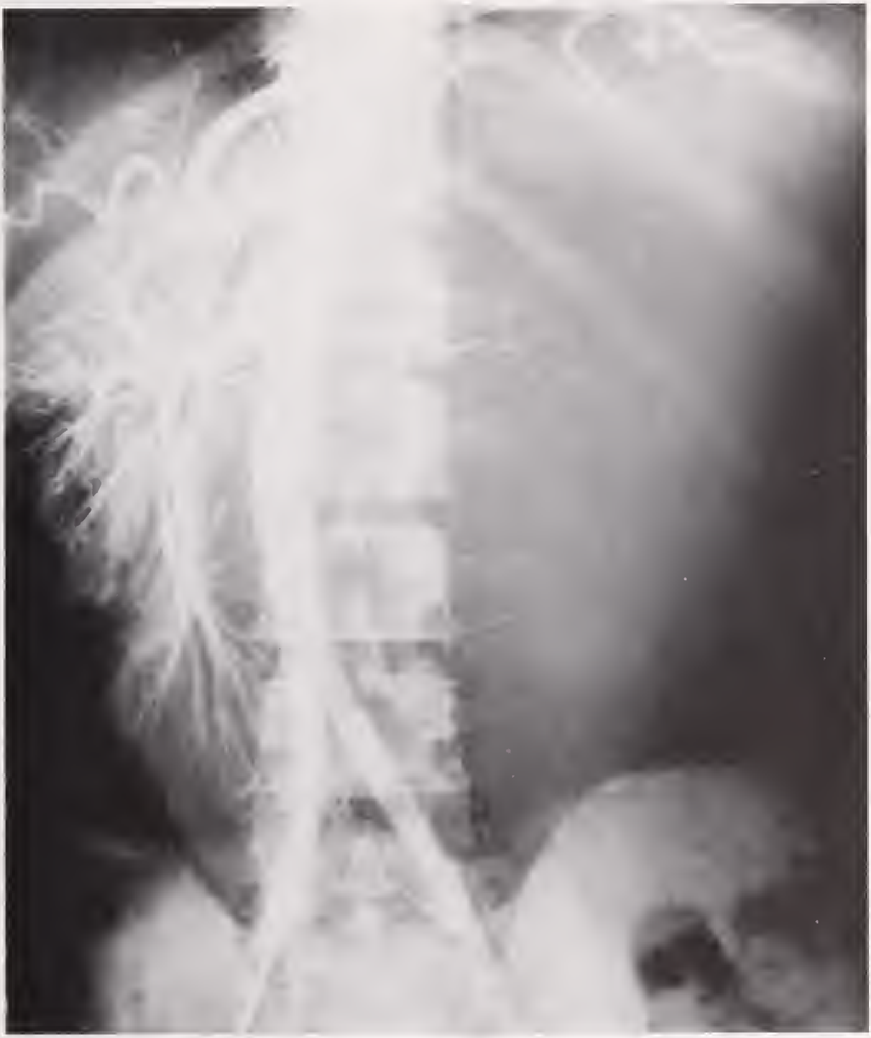
* From the Department of Radiology, Grant Hospital of Chicago, Chicago, Illinois; and Stritch School of Medicine, Loyola University, Maywood, Illinois.



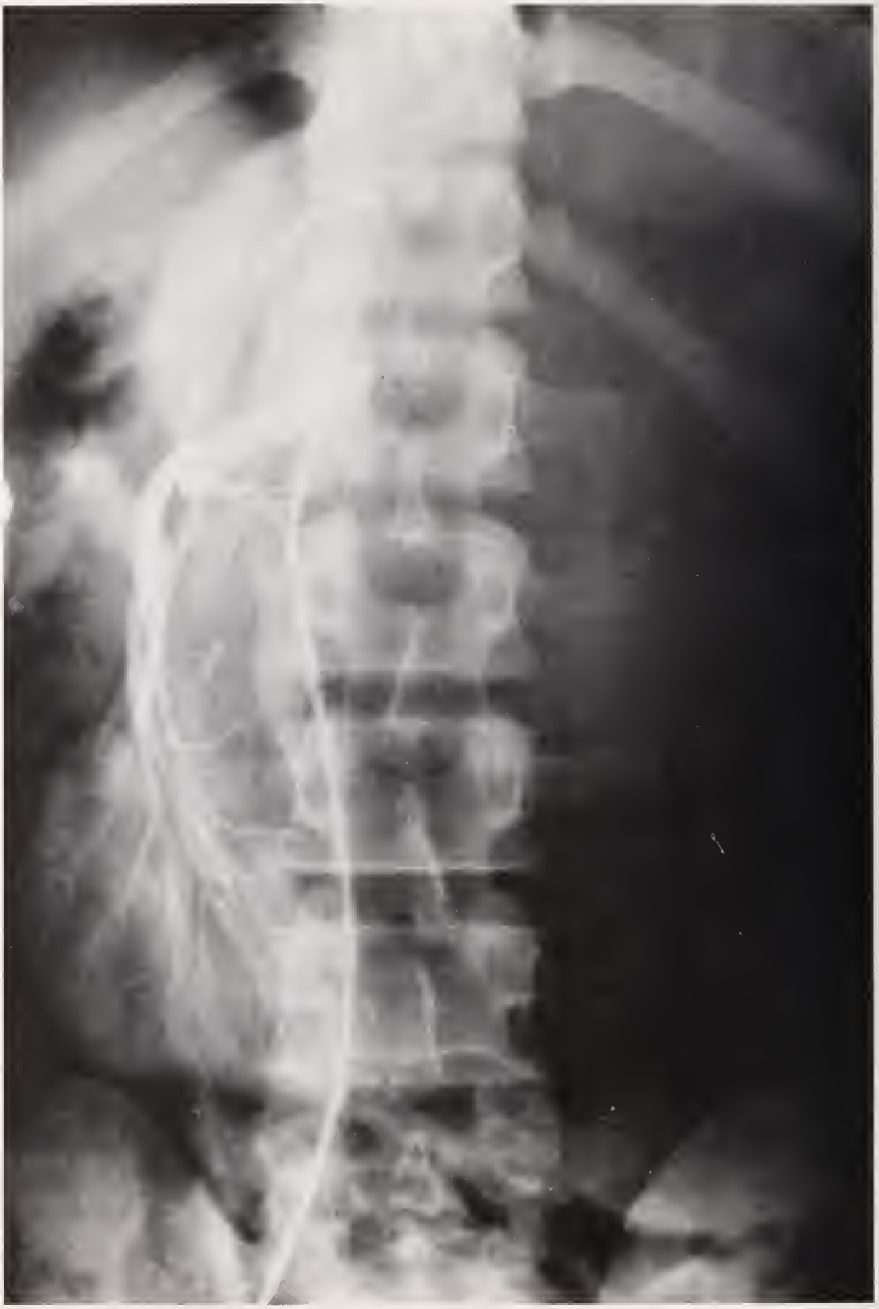
Case 394, Fig. 1. Intravenous pyelogram, in the frontal projection, reveals a huge left abdominal mass with contralateral displacement of the left kidney.



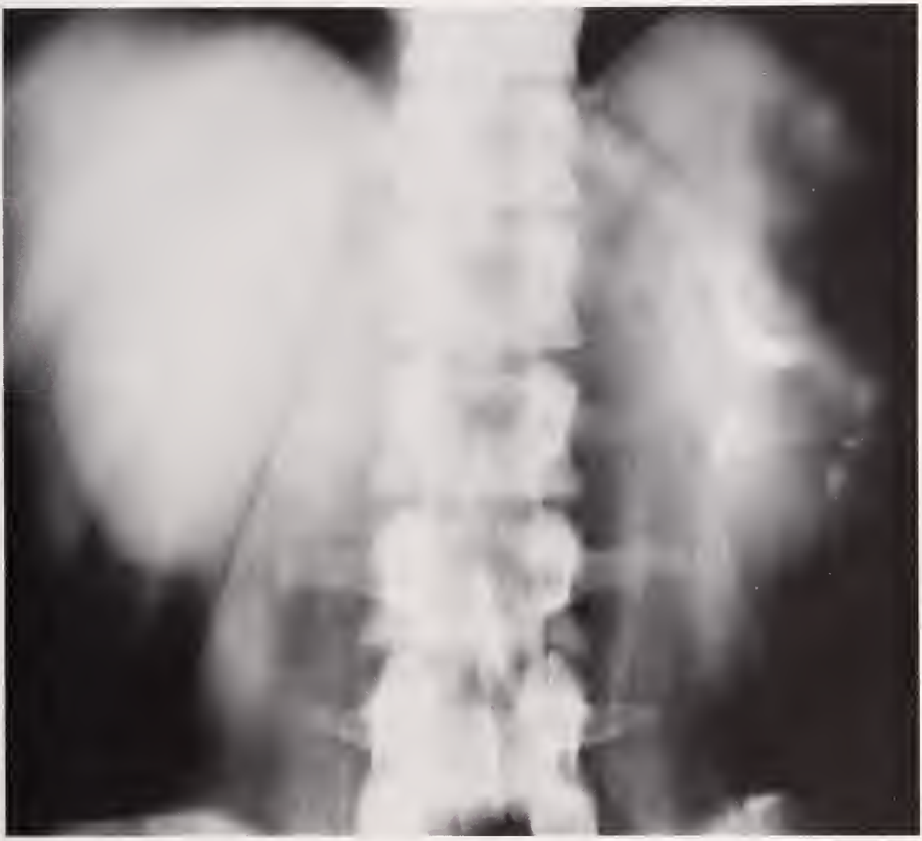
Case 394, Fig. 2. Gastrointestinal study with barium outlining the stomach and small bowel demonstrates displacement of the stomach to the right and the small bowel downwards and to the right by the left upper quadrant mass. The splenic flexure is also noted to be pushed downwards by the mass lesion.



Case 394, Fig. 3. Aortogram reveals the abdominal aorta and its major branches to be displaced toward the right side. The splenic artery is also displaced superiorly; the left renal artery is noted in the right paralumbar region.



Case 394, Fig. 4. Selective left renal arteriography (right paralumbar location) with a deformity of the left kidney bordering a large avascular mass.



Case 394, Fig. 5. Nephrotomography eight months after surgery demonstrates a return of the left kidney into a normal position, with only a small deformity of its collecting system.

Discussion

Giant solitary, benign renal cysts in the adult with contralateral renal displacement are rare. Four cases have been reported. Woesner et al presented two cases and reviewed two in previous literature (1).

Pronounced displacement of a kidney usually occurs in the presence of a benign retroperitoneal tumor or one of low grade malignancy (1). However, marked renal displacement can also occur in the presence of extreme liver or spleen enlargement. Intraperitoneal mass, lesions and, rather rarely, renal or adrenal carcinoma may produce this finding.

Thus, in the presence of contralateral renal displacement, surgical excision of the causative mass is often feasible. In the presence of a giant renal cyst, surgical prognosis is excellent.

Case Report: GIANT RENAL CYST.

Reference

1. Woesner, M. E., Lang, D. W., and Selvaggi, F. P.: Contralateral Displacement of the Kidney by Solitary Renal Cyst, Am J Roentgenol 116:766–772, 1972.

Case No. 395

*Submitted by**

GEORGE HERMANN, M.D. AND YALE ROSEN, M.D.

A 37-year-old woman noticed a painful swelling in the area of the left distal clavicle for about three weeks. The mass measured approximately 3 × 4 × 6 centimeters in size and was located over the antero-superior aspect of the left clavicle. It was firm, slightly movable and nontender. The previous history was noncontributory. Laboratory examination failed to reveal any abnormality. Radiologic examination of the left shoulder showed a 4 × 6 centimeter oval mass located at the distal third of the clavicle. The mass showed coarse calcified densities intermingled with areas of radiolucencies (Fig. 1A). The periphery of the mass was sharply outlined and separated from the surrounding tissues. The lesion was not attached to the clavicle (Fig. 1B). No erosive processes were seen within the clavicle. At operation, a hard encapsulated, nonadherent mass was removed from the left supraclavicular area. The resected specimen was an ovoid fatty mass measuring 5 × 2 × 2.5 centimeters. Numerous small gritty calcified areas were seen on the cut surface. Microscopically, the mass was seen to be composed of mature benign appearing adipose tissue. Scattered throughout were small spicules of mature bone (Fig. 2A). Many of the bone spicules exhibited periosteum-like plaques of fibrous connective tissue adherent to one of their surfaces. Rare foci of cartilage were also seen (Fig. 2B).

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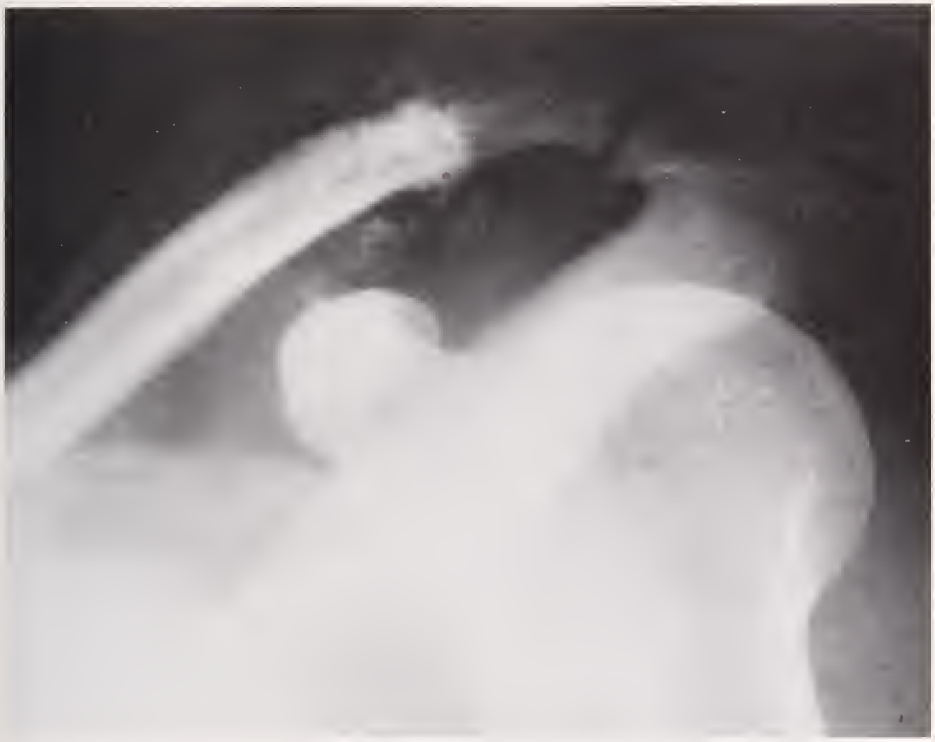
* From the Department of Radiology, Mount Sinai School of Medicine of The City University of New York, N.Y.; and the Department of Pathology, State University of New York, Downstate Medical Center and Kings County Hospital Center, Brooklyn, N.Y.



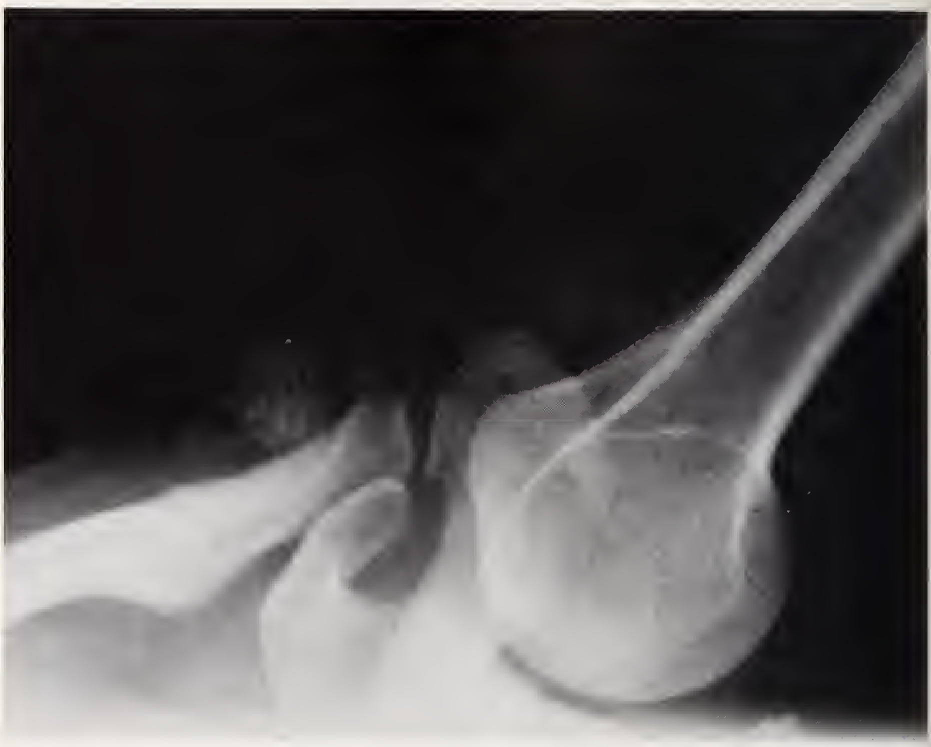
Case 395, Fig. 1 A: Antero-posterior view of the left clavicle demonstrates a sharply demarcated translucent mass containing multiple coarsely calcified plaques overlying the distal third of the clavicle. The underlying bone is normal.

Discussion

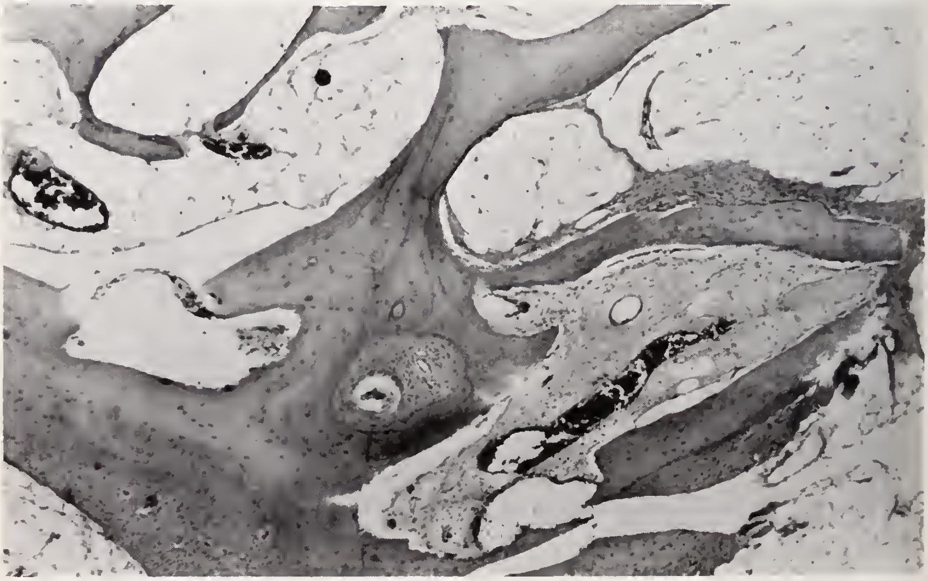
The finding of bone within a lipoma is rare. In 1959 Plaut reviewed the literature for the preceding 50 years and found only four histologically documented cases. In addition, he described three more cases of lipomas with bone and cartilage, all arising in the soft tissues of the extremities. In 1952, Jacobs described two cases of periosteal lipoma with hyperostosis. One of the lesions was said to contain an irregular bony structure. Since there was no histologic documentation of these two cases, it was not possible for us to determine their true nature. The origin of bone in a lipoma is not clear. It may represent a metaplastic process or in these rare cases, the bone and cartilage may represent independent elements indigenous to the tumor from the time of its inception.

Radiographically, lipomata usually appear as a well-defined radiolucent zone encircled by a radiopaque shadow which is separate from the surrounding tissue. The additional finding of calcific densities within the mass, as seen in our case, should suggest the possibility of ossifying lipoma.

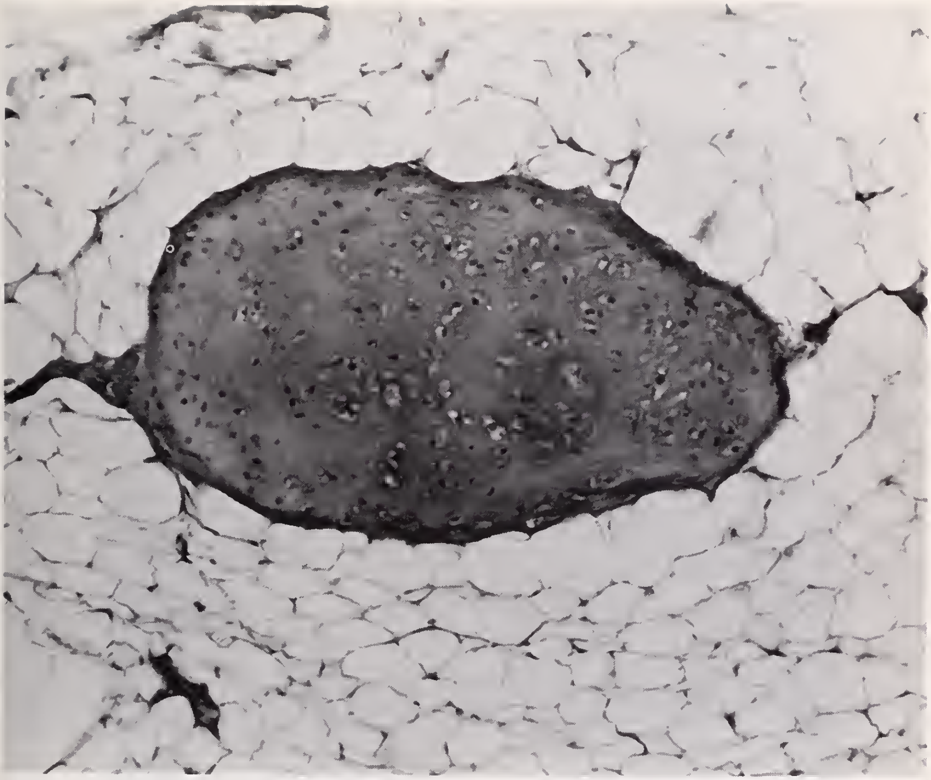
The radiologic differential diagnosis of ossifying lipoma includes calcinosis, bursal calcification, myositis ossificans and juxta-ossal calcified tumor (4). The lesion of tumoral calcinosis is usually related to the extensor surfaces of



Case 395, Fig. 1 B: Tangential view of the mass shows the lesion above the clavicle and independent of the bone.



Case 395, Fig. 2 A: Photomicrograph demonstrates spicules of mature bone with focal plaques of adherent fibrous periosteum-like tissue (H & E × 40).



Case 395, Fig. 2 B: A high-power view shows a rare focus of cartilage surrounded by fat (H & E × 63).

joints and most commonly is seen involving the hip, buttock, elbow, and shoulder. The dense pattern of calcification seen in tumoral calcinosis is in marked contrast to the finer trabecular pattern of calcification in ossifying lipoma (1, 3). Bursal calcification exhibits a coarse pattern of calcification and the lesions are found at the anatomical location of bursae. Juxta-cortical cartilagenous and bony tumors can be easily differentiated from ossifying lipomata by their radiologic and clinical characteristics. Myositis ossificans shows a typical well organized pattern of ossification which often develops following injury (6).

Case Report: OSSIFYING LIPOMA

References

1. Barton, D. I. and Reeves, R. J.: Tumoral Calcinosis, Report of Three Cases and Review of the Literature, Amer J Roentgenology and Radium Therapy 86:351–358, 1961.
2. Jacobs, P.: Periosteal Lipoma with Hyperostosis, Clin Radiology 23:196–198, 1972.
3. McClatchie, S. and Bremner, A. D.: Tumoral Calcinosis—An Unrecognized Disease, Brit Med J 1:153–155, 1969.
4. Murphy, N. B.: Ossifying Lipoma, Brit J Radiology 47, 97–98, 1974.
5. Norman, A. and Dorfman, H. D.: Juxtacortical Circumscribed Myositis Ossificans: Evolution and Radiographic Features, Radiology, 96: 301–306, 1970.
6. Plaut, G. S., Salm, R., and Truscott, D. E.: Three Cases of Ossifying Lipoma, J Pathol Bacteriol 78: 292–295, 1959.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

OPHTHALMOLOGIC NOTES

KEITH M. ZINN, M.D., EDITOR

Reversible Hypertensive Retinopathy

Submitted By

JOHN PALUMBO, M.D. AND KEITH M. ZINN, M.D.

The resoution of hypertensive retinopathy secondary to renal disease has been well documented in the literature (1–4). After nephrectomy, all patients undergo spontaneous remission of their retinopathy with gradual clearing of their hemorrhages, "cotton wool" spots, and papilledema. The vision also gradually returns.

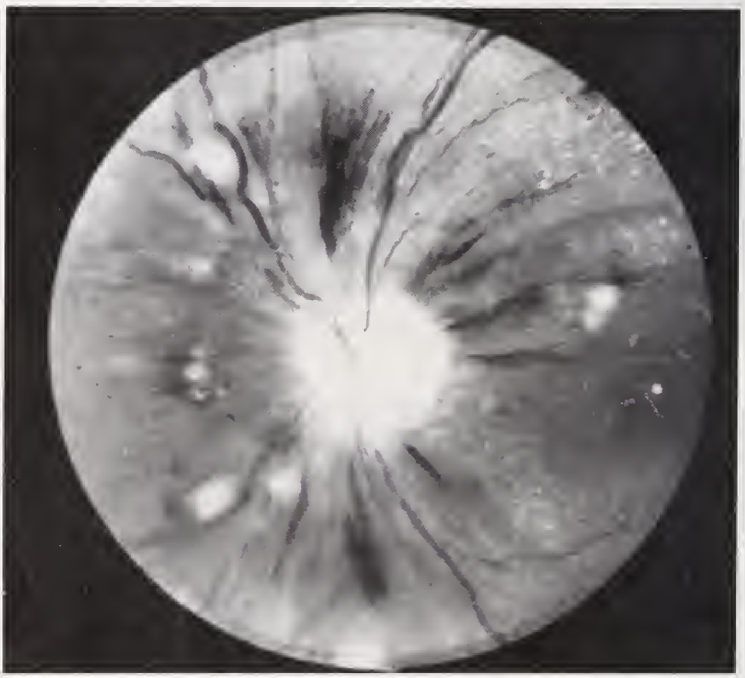


FIG. 1. Fundus photograph of left eye with hypertensive retinopathy. Splinter hemorrhages and cotton-wool spots are present about the optic nerve head. A macular star is also present. Marked arteriolar narrowing and A-V crossing defects are also present.

Recently. we were fortunate to be able to follow just such a case. The

From the Department of Ophthalmology, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Keith M. Zinn, M.D.,1044 Fifth Avenue, New York, N. Y. 10028.

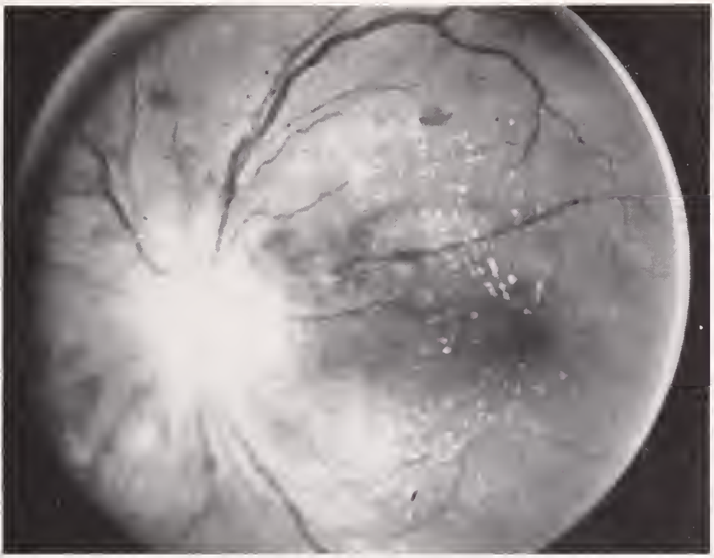


FIG. 2. Fundus photograph of the left eye of patient three weeks postnephrectomy. Resolution of splinter hemorrhages and cotton wool spots has begun. Remnants of the macular star still remain.

patient was a 44-year-old Hispanic male who four years prior to our initial examination experienced Raynaud's phenomena. Three years prior to examination, the patient developed a diffuse macular rash on his back and extremities, hypertension, and renal disease with rising BUN and creatinine levels. A year prior to examination, the patient was on dialysis and had a presumptive diagnosis of scleroderma.

At the time of our examination, the patient complained of decreased vision for the last three months. He was on Aldomet, 1.5 gm/day and thrice weekly dialysis. His blood pressure was in the 160–190/90–110 mm Hg range.

Visual acuity in the right eye was 20/400 and 5/400 in the left eye. Extraocular movements were full with normal saccades and pursuits. The pupils reacted equally to light and accommodation. There were no relative afferent pupillary defects noted. Examination of the lids, conjunctiva, cornea, iris, lens, and vitreous were normal. Intraocular pressure, by applanation tonography, was 15 mm Hg in the right eye and 14 mm Hg in the left eye.

The fundus picture (Fig. 1) showed at least grade 4 hypertensive retinopathy with arterial narrowing, flameshaped hemorrhages, infarcts in the nerve fiber layer of the retina (cotton-wool spots), papilledema, diffuse retinal edema, as well as old, hard, small, yellowish exudates.

One week after our initial examination, the patient underwent bilateral nephrectomy. The visual acuity two weeks postoperatively was 20/70 in both eyes. Three weeks post nephrectomy the visual acuity was 20/40+ in both eyes and the fundus picture showed a drastic improvement (Fig. 2). The superficial hemorrhages were almost completely resolved as were the cotton-wool spots. The papilledema receded (not readily demonstrated in two-dimensional photograph). Only the arterial changes and hard exudates remained.

This case is instructive to the ophthalmologist and internist as a reminder that the retinal changes of malignant hypertension secondary to certain diseases are reversible. The physician who encounters malignant hypertensive retinopathy must rule out renal disease, e.g., pyelonephritis, glomerulonephritis, and toxemia, as well as other disorders, including coarctation of the aorta, pheocromocytoma and tumors of the adrenal cortex that can give rise to Cushing's syndrome.

References

1. Lockhart, G., von Noorden, G., Dustan H. P., Corcoran, A. C., and Page, I.H: The Course of Retinopathy in Treated Malignant Hypertension, **Arch Intern Med** 106:205, 1960.
2. Fonken, H. A. and Ellis, P. P.: Retinopathies of Chronic Renal Disease **Ann Intern Med** 62:499, 1965.
3. Ellis, P. P. and Fonken, H. A.: Retinopathy of Chronic Glomerulonephritis **Arch Ophthal** 75:36, 1966.
4. Donohue, J. P., Bohnert, W., Shives, D. L., and Bradley, K. P.: Bilateral Nephrectomy: Its Role in Management of the Malignant Hypertension of End-Stage Renal Disease, **J Urol** 106:488, 1971.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

NEUROLOGIC-NEUROSURGICAL NOTES

JOHN LUSINS, M.D. AND MARTIN H. SAVITZ, M.D., COEDITORS

Acute Cerebellar Infarction Producing Brainstem Compression

Submitted By

MARTIN H. SAVITZ, M.D., S. SHELDON KATZ, M.D., AND HIROSHI NAKAZAWA, M.D.

Infarction of the cerebellum in the distribution of the posterior inferior cerebellar artery rarely is seen as an isolated syndrome, since the intrinsic vasculature of the medulla is commonly involved. Cerebellar softening and swelling with secondary compromise of the brainstem rapidly leads to coma and death without appropriate treatment; immediate surgical decompression of the posterior fossa was an effective lifesaving procedure in only nine previously reported cases (1–5). The purpose of this paper is to report one additional case of acute cerebellar infarction, in which the clinical signs and symptoms were well documented and in which the resulting brainstem compression was successfully relieved by suboccipital craniectomy.

Case Report

A 60-year-old man had sudden onset of occipital cephalgia, rotary dizziness, and imbalance with a tendency to fall toward the right side. Past medical history elicited emphysema for over 10 years. Initial neurologic testing demonstrated right facial weakness, dysarthria, dysmetria, dysdiadokokinesia, and nystagmus on right lateral gaze. Funduscopic examination revealed mild arteriosclerotic changes. Four hours after admission to the intensive care unit, obtunded mental status, pinpoint pupils, decerebrate posturing, and bilateral Babinski signs were noted.

The patient was intubated and required assistance by a mechanical respirator. Dexamethasone 10 mg was given intravenously. An emergency right brachial angiogram demonstrated a tight posterior fossa with kinking of the aqueduct (Figs. 1A and 1B). Intravenous fluids were restricted; 200 cc of mannitol 20% was given and then repeated in 4 hours. Twelve hours after admission, he became arreflexic and unresponsive to deep pain; all spontaneous respiration ceased. A left brachial angiogram demonstrated that the circulation of contrast medium was quite slow due to increased intracranial pressure; vascular detail was lacking.

Suboccipital craniectomy was performed with the patient in the sitting position. The dura was tense; and after the opening, the cerebellum appeared

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From the Departments of Surgery and Pathology, Nyack Hospital, Nyack, New York.

Requests for reprints should be sent to: Dr. Martin H. Savitz, 30 South Cole Avenue, Spring Valley, N.Y. 10956.

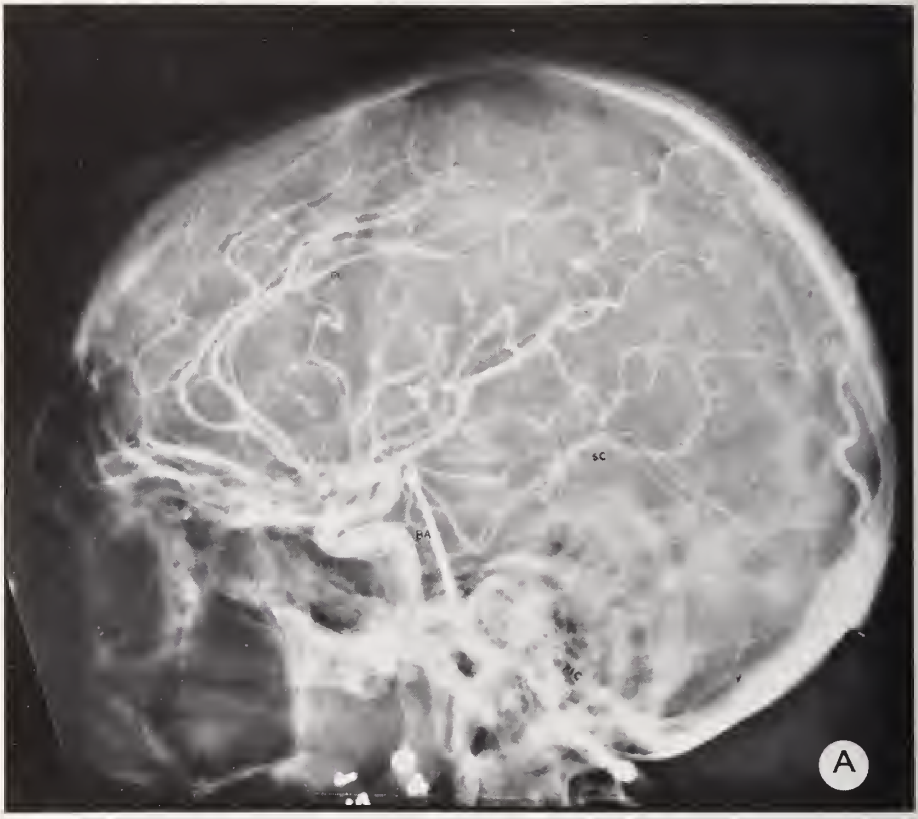

FIG. 1A. Right brachial angiogram, arterial phase. Note broad sweep of pericallosal artery (PC) indicating hydrocephalus, elevation of superior cerebellar artery (SC) related to vermis, displacement of basilar artery (BA) toward clivus; also note posterior inferior cerebellar artery (PIC) proximal portion related to tonsil downward and forward, vermian segment (V) displaced posteriorly and inferiorly.

markedly swollen with widened folia, especially on the right side. The right cerebellar hemisphere was explored, and no hematoma was found. Frozen section of the cortex and white matter revealed no neoplasm, only edema and hemorrhagic necrosis (Fig. 2). The lateral third of the right hemisphere was resected, and pulsations were then observed in the posterior fossa structures.

In the immediate postoperative period, spontaneous respirations were recorded; pupillary and corneal reflexes were present. Dexamethasone therapy was slowly tapered over a 5 day period. A tracheostomy was performed. By the tenth postoperative day, there were voluntary movements in all limbs. The patient took cognizance of his surroundings during the third postoperative week. Significant findings on neurologic examination were left abducens palsy, diminished right gag reflex, and left hemiparesis.

A gastrostomy was performed for feeding purposes and maintained until the third postoperative month. Three episodes of Staphylococcus aureus pneumonia were treated with appropriate antibiotics. At four months, the tracheostomy and gastrostomy tubes were removed. Dysphagia and dys-

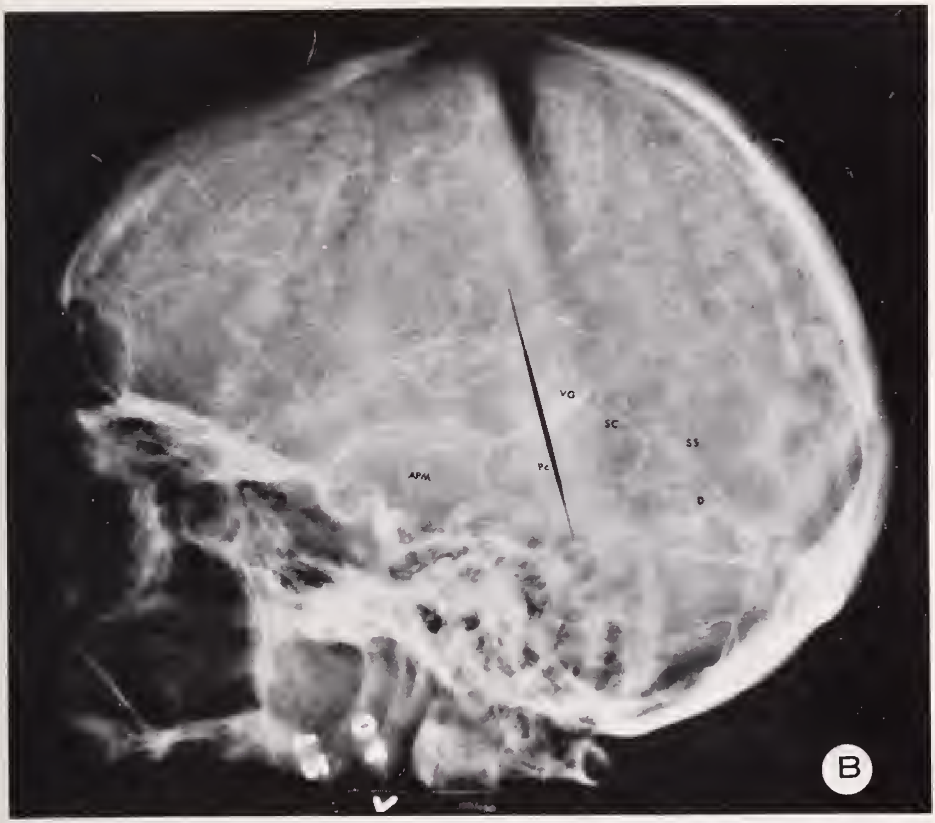

FIG. 1B. Right brachial angiogram, venous phase. Note anterior pontomesencephalic vein (APM) displaced upward and forward, forward displacement of precentral cerebellar vein (PC), supraculminate vein (SC) arched upward close to vein of Galen (VG) and straight sinus (SS) indicating narrowing of superior cerebellar cistern; also note declival vein (D) displaced upward and psteriorly close to straight sinus (SS), inferior vermian vein not visualized.

phonia persisted. The patient was transferred to a rehabilitation facility. At six months, he was fully ambulatory, independent in the activities of daily living, and able to be discharged home. One year after his surgery, the left abducens paralysis has not resolved.

Discussion

A wedge-shaped infarct of the lateral aspect of the medulla and the inferior surface of the cerebellum is sometimes caused by occlusion of the posterior inferior cerebellar artery, but is more often due to thrombosis of one vertebral artery (6). Unlike the lateral medullary syndrome, manifestations of cerebellar disturbance are not immediately overshadowed by brainstem signs in cases of cerebellar infarction. Subacute spontaneous cerebellar hemorrhage, posterior fossa subdural hematoma, or primary cerebellar neoplasm may present with similar symptoms and signs (7).

Fairburn and Oliver (7) and Lindgren (2) were the first to call attention to cerebellar infarction as a neurosurgical emergency requiring prompt de-

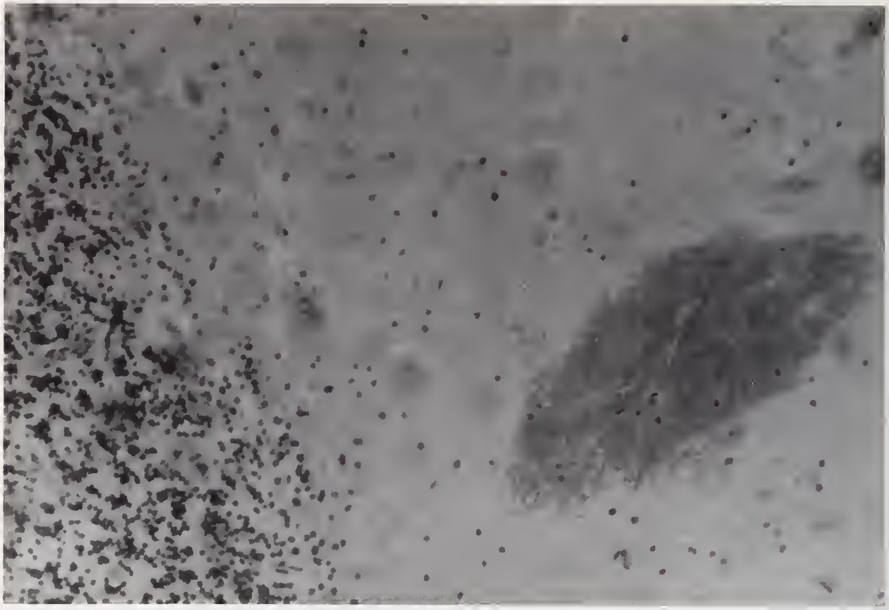

FIG. 2. Cerebellum with areas of edema, hemorrhage, and necrosis (H & E × 320).

compression and resection of edematous and necrotic tissue. Lehrich et al (5) reviewed sixteen cases of cerebellar infarcts with ensuing compromise of the medullary vital centers. Duncan et al (6) analyzed three additional cases. Thirteen patients underwent suboccipital craniectomy during the acute phase of cerebellar softening and swelling; one patient was explored as a tumor suspect after recovering from coma. Sixteen of these nineteen patients were males; the ages ranged from 36 to 78, with a mean of 56 years.

Old or recent infarction of one cerebellar hemisphere is a commonplace autopsy finding, but the diagnosis is rarely made while the patient is alive. Ventriculography was the primary method of investigation in most reported cases. Carotid angiography, and to a much lesser extent direct vertebral angiography, was performed in some cases. Retrograde brachial angiography generally provides adequate opacification of the vertebrobasilar system (8). Computerized x-ray scanning of the brain will also aid in the differential diagnosis of a posterior fossa mass (9).

Summary

A case of acute cerebellar infarction producing brainstem compression is reported. The differential diagnosis, methods of investigation, and neurosurgical treatment are discussed. A brief review of the literature is presented.

Acknowledgment

The authors wish to express their gratitude to Professor Yun Peng Huang, who reviewed the cerebral aniography and prepared the illustrations.

References

1. Fairburn, B. and Oliver, L. C.: Cerebellar Softening: A Surgical Emergency, Brit Med J 1:1335–1336, 1956.
2. Lindgren, S. O.: Infarctions Simulating Brain Tumours in the Posterior Fossa, J Neurosurg 13:575–581, 1956.
3. Pomme, B.: Le ramollissement pseudotumoral du cervelet: à propos de deux observations, Sem Hop Paris 35:791–793, 1959.
4. Wood, M. W. and Murphey, F.: Obstructive Hydrocephalus Due to Infarction of a Cerebellar Hemisphere, J Neurosurg 30:260–263, 1969.
5. Lehrich, J. R., Winkler, G. F., and Ojemann, R. G.: Cerebellar Infarction with Brainstem Compression, Arch Neurol 22:490–498, 1970.
6. Duncan, G. W., Parker, S. W., and Fisher, C. M.: Acute Cerebellar Infarction in the PICA Territory, Arch Neurol 32:364–368, 1975.
7. Hollin, S. A., Decker, R. E., and Gross, S. W.: Spontaneous Cerebellar Hematomas, Mount Sinai J Med 41: 396–406, 1974.
8. Pygott, F., Hutton, C. F.: Vertebral Arteriography by Percutaneous Brachial Artery Catheterization, Brit J Radiol 32:114–115, 1959.
9. Ambrose, J.: Computerized X-ray Scanning of the Brain, J Neurosurg 40:679–695, 1974.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

PEDIATRIC NOTES

AARON R. RAUSEN, M.D., EDITOR

Elevated Epstein-Barr Antibodies in an Infant with Hepatitis

Submitted By

SAMUEL H. SILVERMAN, M.D. AND YASHAR HIRSHAUT, M.D.

The causative agent of infectious mononucleosis (IM) has not been ascertained. The Epstein-Barr virus (EBV) frequently associated with Burkitt's lymphoma (1), cancer of the nasopharynx (2), and sarcoidosis (3), has been implicated in its etiology but Koch's postulates remain to be fulfilled. It is generally agreed, however, that the appearance of antibody to EBV is a sentinel of IM. This was first shown by the Henles and Diehl (4) in 1968 and was subsequently confirmed by others (5-7). The heterophile antibody is also associated with IM and remains the diagnostic test most commonly employed. Unfortunately, it is not usually positive in children less than four years of age (8, 9) even when all other criteria of IM are present.

An infant with possible congenital IM is described. His clinical appearance, hematologic findings and serologic data are compared to those described in older patients.

Case Report

F. S., a Hispanic male infant, was the product of the second pregnancy of a serology negative 18-year-old mother. The mother had an uneventful pregnancy and postpartum period. The mother was group O, Rh positive. The infant was group B, Rh negative. The direct and indirect Coombs' tests in the infant's blood were negative. At 61 hours of life, the child had a serum total bilirubin concentration of 15 mgm% and a serum direct-reacting bilirubin concentration of 1.2 mgm%. The infant received phototherapy for 30 hours and was discharged on the eighth day of life. On the tenth day of life, his serum total bilirubin concentration was 4 mgm%. The hyperbilirubinemia was ascribed to presumptive BO hemolytic disease of the newborn. There was no history of exposure to chemical hepatotoxins.

At ten weeks of age, the infant was admitted to the hospital with asymptomatic recurrent jaundice. A tender liver edge was palpated 6 cm below the right costal margin. No other organ enlargement or adenopathy was noted. The child had no evidence of a rash during his illness. The stool was of normal

From the Departments of Pediatrics, Beth Israel Medical Center; and Mount Sinai School of Medicine of the City University of New York, New York; and the Department of Medicine, Cornell University Medical Center, New York, New York.

Requests for reprints should be sent to: Dr. Samuel H. Silverman, Department of Pediatrics, Beth Israel Medical Center, New York, N.Y. 10003.

color. Bile and urobilinogen were found in the urine. The hemoglobin was 10.8 gm/100 ml, hematocrit 32.4%, red blood cell count 3.67 million/mm^3, reticulocytes 2.1%. The white blood cell count was 20,100/mm^3, with polymorphonuclear leucocytes 23%, lymphocytes 74%, monocytes 2%, eosinophils 1%. Platelets were adequate. None of the lymphocytes were atypical. The sedimentation rate (Westergren) was 92 mm/hour. Electrolytes were normal. Serum total bilirubin concentration was 5.6 mgm%. Prothrombin time was 12.7 seconds with a control of 11.8 seconds. The partial thromboplastin time was 29.6 seconds, the control 30.2 seconds. Total protein was 8.8 gm/100 ml, albumin 5.5 gm/100 ml, calcium 10 mgm/100 ml, phosphorus 7 mgm/100 ml, alkaline phosphatase 460 mμ/ml, total cholesterol was 290 mgm%, SGOT 170 mμ/ml, creatinine 0.6 mgm/100 ml. X-rays of the skull, chest and long bones were normal.

Two days later, the serum total bilirubin concentration had decreased to 3.7 mgm% and the serum direct bilirubin concentration was 3 mgm%, SGOT 284 mu/ml and SGPT 52 mμ/ml. Five days after admission, the SGOT was 305 mu/ml, SGPT 103 mu/ml and the mono spot test was positive. The heterophile antibody was negative, Hepatitis B Surface antigen by immunoelectrophoresis was negative, alpha-1 antitrypsin 350 mg/100 ml (normal 210–500), alpha fetoprotein was positive. The VDRL was negative, cytomegalovirus, rubella and herpes hominis antibody titers were negative. The EBV antibody titer was positive 1:160. The sequence of EBV antibodies in the patient and his mother is noted in Table I. The father, mother, and a sibling had normal SGOT levels and were negative for Hepatitis B Surface antigen.

Within two weeks after admission, the jaundice disappeared. Six weeks after admission, the child's liver was of normal size. The child continued asymptomatic. Five months after admission, the SGOT remained elevated at 129 mμ/ml. The child's growth has been above the 70th percentile from birth until the present time (eighteen months of age.) The patient was lost to followup at 19 months of age so that subsequent serum alpha fetoprotein and SGOT determinations were obtained.

Discussion

The diagnosis of IM is based on four cornerstones: the clinical picture; the presence of atypical lymphocytes in the peripheral blood smear; a positive heterophile; and antibody to the Epstein-Barr virus. The clinical picture of IM in a preschool child is frequently atypical (8, 10). Of the clinical findings of IM as we know them, i.e., exudative tonsillitis, lymphadenitis, hepatosplenomegaly, and fever, our patient had only hepatitis, a known complication of

Table I

Epstein-Barr virus antibody titers in infant and mother

Age of infant in days	F.S.	Mother
93	1:160	–
151	1:40	1:640
241	1:160	1:160

IM. On admission, at ten weeks of age, he had lymphocytosis with no atypical lymphocytes. This was accompanied by chemical evidence compatible with hepatitis.

In this case, the diagnosis of a viral hepatitis at age ten weeks appears to be supported by the transient hepatomegaly, lymphocytosis and chemical abnormalities. The "mono spot" test results were suspicious of IM but not diagnostic. Most interesting are the EBV antibody titers. Shapiro et al (11) have shown that EBV antibody acquired transplacentally from the mother at birth is generally cleared from the infant's circulation by age six months. If the antibody is again detected, there is indication of acquired infection with EBV. On repeated testing, F.S. has continued to show serum reactivity to this virus. This is presumptive evidence that the infant was infected with EBV during or shortly after birth. Accepting the statement of Hoagland (9) that the incubation period of IM is 35 to 60 days, the occurrence of jaundice at ten weeks might well have coincided with clinical disease produced by the IM virus transmitted from mother to child at birth or soon thereafter.

The serologic diagnosis of IM is based on the determination of two antibodies; a heterophile antibody which is an IgM antibody and cannot pass through the placenta and the EBV antibody which is an IgG antibody which can be placentally transmitted. In older children and adults with IM, the appearance and persistence of the EBV antibodies is closely associated with the clinical illness. On admission, our patient had an increased titer of EBV antibodies (1:160). Fifty-eight days later, his titer dropped to 1:40, suggesting disappearance of transplacental antibody. Subsequently, our infant had a persistent immune response to EBV as did Tamir's (12) young patient. This pattern may be common for the very young with IM. The Paul-Bunnell-Davidsohn test was negative in our patient as is usually reported under the age of four years (13). The "mono" test, which is more sensitive and less specific (14), was positive on three separate occasions. EBV antibody titers have remained significantly elevated from age 93 days to 241 days.

Twenty years ago, IM was considered to be a rare illness. Evans (15) recently stated that it is the third most frequently reported communicable disease. The peak frequency of IM is between 15 to 25 years of age. Since this is the reproductive age group, on the basis of incidence, one should expect to see cases of congenital IM, although no such patient has been documented in the literature. In particular, the observations of jaundice in the first two or three months of life might indicate the possibility of congenital IM hepatitis. Pediatricians should be alert to the possibility that unusual symptom complexes induced by viruses before 5 years of age may be caused by agents which later in life cause more readily recognized disease syndromes.

Summary

A ten-week-old infant presented with asymptomatic hepatitis accompanied by lymphocytosis, a positive "mono spot" test and persistent elevation of Epstein-Barr virus (EBV) antibody titers. This appears to have been a case of infectious mononucleosis (IM) acquired during or soon after birth.

BIBLIOGRAPHY

1. Henle, G. and Henle, W.: Immunofluorescence in Cells derived from Burkitt's Lymphoma, J Bact 91:1248, 1966.
2. Old, L. J., Boyse, E. A., Oettgen, H. F., deHarven, E., Geering, G., Williamson, B., and Clifford, P.: Precipitating Antibody in Human Serum to an Antigen Present in Cultured Burkitt's Lymphoma Cells, Proc Nat Acad Sci 56:1699, 1966.
3. Hirshaut, Y., Glade, P., Viera, L. O. B. D., Ainbender, E., Dvorak, B., and Siltzbach, L. E.: Sarcoidosis, Another Disease associated with Serological Evidence for Herpes-Like Virus Infection, N Engl J Med 283:502, 1970.
4. Henle, G., Henle, W., and Diehl, V.: Relation of Burkitt's Tumor Associated Herpes-Type Virus to Infectious Mononucleosis, Proc Nat Acad Sci 59:94–101, 1968.
5. Niederman, J. C., McCollum, R. W., Henle, G., and Henle, W.: Infectious Mononucleosis: Clinical Manifestations in Relation to EB Virus Antibodies, JAMA 203:205–209, 1968.
6. Diehl, V., Henle, G., Henle W., and Hohn, G.: Demonstration of Herpes Group Virus in Cultures of Peripheral Leucocytes from Patients with Infectious Mononucleosis, J Virol 2:663–9, 1968.
7. Hirshaut, Y., Glade, P., Moses, A., Manaker, R., and Chessin, L.: Association of Herpes-Like Virus Infection with Infectious Mononucleosis, Am J Med 47:520, 1969.
8. Evans, A.: Infectious Mononucleosis in University of Wisconsin Students, Am J Hygiene 71:342, 1960.
9. Hoagland, R. J.: Infectious Mononucleosis. Grune and Stratton, Inc., New York, 1967.
10. Starling, K. A., and Fernbach, D. J.: Infectious Mononucleosis in the Preschool Child, JAMA 203:294, 1968.
11. Shapiro, L. R., Hirshaut, Y., Kawef, D. M., and Glade, P.: Epstein-Barr Virus in Infancy, J Ped 80:1025, 1972.
12. Tamir, D., Benderly, A., Levy, J., Ben-Porath, E., and Vansover, A.: Infectious Mononucleosis and Epstein-Barr Virus in Childhood, Ped 53:330, 1974.
13. Davidsohn, L., Stern, K., and Kashiwagi, C.: The Differential Test for Infectious Mononucleosis, Am J Clin Path 21:1101, 1951.
14. Fernbach, D. J., and Starling, K. A.: Infectious Mononucleosis, Ped Clin N Amer 19, No. 4, 957, 1972.
15. Glade, P.: *Infectious mononucleosis,* J. B. Lippincott Co., Philadelphia 1973, p. 38.

The Mount Sinai Journal of Medicine
Vol. 44, No. 2, March-April, 1977
Printed in U.S.A.

THE STUDENT'S CORNER

ALEXANDER AMBROZ, B.S., Editor

This column is a forum for medical students to comment on issues concerning medical school and medical education. The editor of this column is a second-year medical student and elected student representative at Mount Sinai School of Medicine of The City University of New York. Mount Sinai School of Medicine students are invited to take advantage of this opportunity to reach a wide and influential readership. Medical students from other schools are also invited to contribute.

Contact Mr. Ambroz through Mount Sinai School of Medicine, The Annenberg Building, Room 13-98A, Fifth Avenue and 100 Street, New York, N.Y. 10029. If you do not have time to write an entire column, you can still contact Mr. Ambroz and share your thoughts on a particular topic which perhaps can be incorporated into a future column.

David A. Dreiling, M.D.
Editor-in-Chief

Competition and Trust: The Medical School Experience

JOHN MORIHISA, M.D.*

There have always been stereotypic qualities and attributes associated with the physician. In fact, a somewhat paradoxical situation is demonstrated by the juxtaposition of the popularity of medical television programs with the unprecedented rise in malpractice suits as well as the increased questioning of medical opinions and the deluge of applicants to medical schools. Perhaps part of these divergent feelings are derived from the role that the physician has in our society. At one time or another every person must place his trust in a physician's knowledge and judgment. The question of trust arises and each physician must find his own style of relating to his patient and gaining their trust. Much of our training provides information and learning situations from which we may obtain the skills not only to heal and alleviate pain but also to understand the suffering of the patient and to communicate about their needs and fears.

However, there is much learning about people that occurs on a level somewhat separate from the doctor-patient relationship. This is in the doctor-doctor relationship and more specifically in the student-student relationship. We learn much from our teachers that will determine not only the way we relate to patients but the ways in which we see ourselves as doctors. However, the interaction between students is perhaps one of the most long lasting and continuous in medical school. It is the least structured and the most variable and therefore has the greatest potential for loss or benefit.

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* Doctor Morihisa graduated from Mount Sinai School of Medicine of The City University of New York in 1976. His comments were submitted to Dr. Sharon Wilkinson (also MSSM 1976), former Student Corner Editor.

The influence of competition has been such an integral part of the pre-med experience that its existence in the medical setting is to some extent predetermined. There are structural factors that can affect an atmosphere of competition in either direction, including pass-fail grading systems and the competition for internship-residency programs. Regardless of the structural determinants, much of the manifestations of competition appears to depend upon the individual. In the same situation different individuals will react very differently to pressures in medical school. The diversity of responses possible has ramifications in terms of the atmosphere created by students that will strike resonance or dissonance with the process of learning. When these individuals are taken as a group their behavior develops a certain flavor and a "class character" emerges.

In each group of medical students there are individuals who represent extremely divergent ways of thinking and ways of approaching medical education. This is as it should be and any loss of asymmetry of opinion would tend to cause a loss in the learning process. However, as each class moves through the four years of training there evolves a "class character." In some cases the individuals in the class do not feel there is any group comradeship. In other classes there has been an esprit de corps, while, in other factions there has been an interface of antipathy. The class character is a generalized essence of the many individual approaches and small group interactions that make up the every day interaction of the medical school class with itself and the medical school. In the past relatively little attention has been paid to this phenomenon and perhaps this is a reflection of the orientation of the medical schools which is primarily to provide high quality health care to people by training skilled physicians. Within this context there is usually the assumption that the doctor-patient relationship is of paramount importance in the delivery of good medical care. However, the relationship among doctors has often been relegated to the artifact of working together for a common good. This is to say that teamwork is necessary in medicine and this implies a working relationship. However, little time is spent on this subject. Perhaps this is because there is an assumption the patient's welfare must transcend all other considerations and that for this reason doctors will work together and with others for the best possible care of patients. As we go through medical school we have all witnessed the unfortunate breakdown of this reasonable logic due to its unreasonable assumptions about human character.

In the medical school class the tensions and competition between medical students represents a continuum that continues throughout professional life. The ways that we work with our compatriots will set patterns of interaction in the future. Thus, it is of value to foster relations that facilitate caring for the patient and minimize tensions between future physicians.

The behavior of individuals is really not at issue here. However, the class character is a different matter. Regardless of the individual action the class character can set the tone of learning as well as determining the degree to which we will work together as doctors. When the class character is one of camaraderie and friendship, misunderstandings and competition have a very different impact. In the class, feelings and thoughts of individuals are modified and often focused by the class character. In a similar manner stressful situations such as examinations and cardiopulmonary arrests can each be strongly predetermined in their effects on individuals, depending on the class character that pervades at the time of crisis.

If an atmosphere of teamwork and friendship has been established, then the crises do not create the kinds of tensions that would be detrimental to the learning of the individual. This is not to say that tension and anxiety should be removed from medical education. These factors are an integral part of the practice of medicine. However, it is important to realize that there is a point after which tension and anxiety begin to prevent learning and actually harm the individual's growth as a person and as a physician. How then can good "class character" be fostered? The problem lies more in the orientation and motivation of students and teachers to see this as a problem which deserves attention rather than in the discovery of a "solution." Indeed it would appear that practically any reasonable approach will meet with some degree of success. Thus, such divergent activities as medical class intramural volleyball to student group study-teaching sessions and regular class meetings (to discuss complaints or plan activities) have all engendered helpful class characters. It would seem that each class would be best able to determine what methods might be useful.

Therefore, the basic problem is in the recognition of the importance of the ways in which students interact and work together. Once this priority is determined the possible "solutions" are of the same order of magnitude as the factorial permutations of the various personality traits and orientations of the people involved.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 2, Mar-Apr, 1977
Printed in U.S.A.

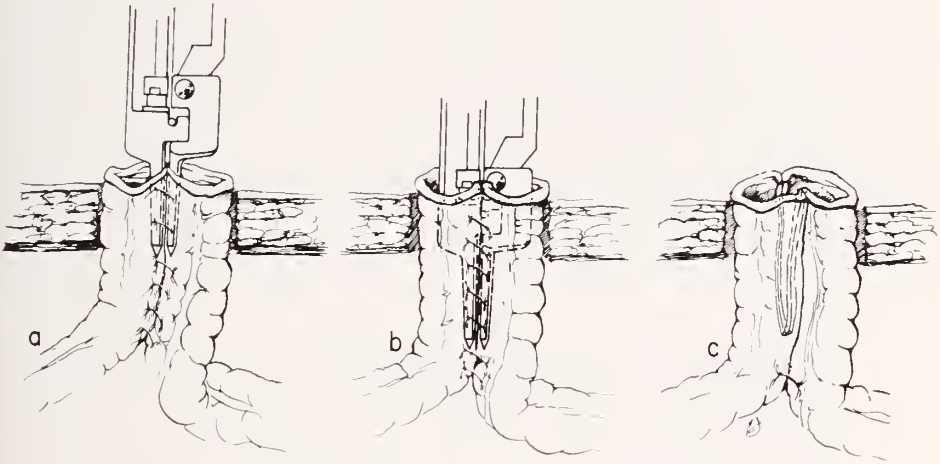
Application of the GIA Stapler Instrument in the Mikulicz Obstructive Resection:

A Brief Communication

HARRY SCHANZER, M.D. AND ABBA A. MESSE, M.D.

As surgeons become more acquainted with stapler instruments, new applications are being described. The present report deals with the use of the GIA instrument (United Surgical Instrument Corp.) for dividing the spur after an obstructive resection prior to closure of colostomy.

In the first case in which we used the GIA instrument, a colostomy closure was being performed following obstructive resection of the sigmoid colon and crushing of the spur by spur crushing clamps. At the time of operation, it was felt that the spur had not been adequately divided, and so further division was performed with one application of the GIA and the colostomy then closed. Subsequently this instrument was then found to be useful in dividing the spur initially, eliminating the necessity of any spur crushing clamps. For an adequate division of the spur it was found that the instrument should be applied twice.



Technique: The instrument may be used either in the Operating Room or at the bedside. After digital examination of the double barrel colostomy confirms that the two adjacent walls are together for sufficient length, the instrument is applied twice as shown in Figure 1 thus creating an immediate opening between the two limbs of bowel measuring about 9 cm in length.

Summary: Obstructive resection is a useful procedure in dealing with perforated, compromised, or obstructed colon. In the past, crushing clamps of

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From the Surgical Service, Bronx Veterans Administration Hospital, 130 West Kingsbridge Road, Bronx, N.Y. 10468.

various types have been used to divide the spur of the double barrel colostomy thus created. This has often required multiple applications to adequately crush the spur, with cumbersome dressings, and delay before the colostomy could be closed.

The use of the GIA instrument, as described here, has proved to be a simple and effective way to divide the spur. It can be performed at the bedside and shortens the interval between initial operation and the closure of the colostomy.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May-June, 1977
Printed in U.S.A.

Introduction

MARVIN S. GILBERT, M.D.

The Mount Sinai Hospital has a long history and tradition as a center of hemophilia care. The rewards, to patients and physicians alike, in the care of a chronic crippling disorder, are few, and it is a credit to these patients and physicians that their association continued until the hematologic advances of the past two decades made possible the "comprehensive care" that will be described in this monograph. Because bleeding may occur into any organ system and because the cost of factor replacement is high, hemophilia places a great strain upon the medical and financial resources of the hospital and community. In 1969 Dr. Louis Aledort and I started a combined Orthopedic-Hemophilia Clinic. Within a few years volunteers from other disciplines joined us and a true "comprehensive care clinic" evolved. The patient and work load steadily increased and at the present time over 180 patients are registered in the clinic. This volunteer staff has remained essentially unchanged over the years. In 1974 the clinic was designated an International Hemophilia Training Center (IHTC) by the World Federation of Hemophilia and soon thereafter it formed a close working relationship with the Hemophilia Clinic at the Cornell University Medical Center. Both clinics rendered primary care to hemophiliacs, but specialty services were set up to avoid duplication of effort in the New York City area. In 1976 a combined grant from the Health Services Administration and the Department of Health, Education and Welfare allowed both institutions to hire a coordinator and a nurse clinician. Data collection forms have been standardized and computerized. A data collector has been added to the staff and a genetics counselor and carrier detection laboratory have been added at Cornell University Medical Center.

The composition of the Mount Sinai Clinic staff will be listed to give an indication of the specialty services that hemophilia care requires:

1. Hematology and Internal Medicine (L.M. Aledort and M. Diaz).
2. Pediatrics (M. Hilgartner at CUMC).
3. Orthopedics (M. Gilbert).
4. Physical Medicine and Rehabilitation (J. Weissman and C. Zottoli).
5. Oral Surgery and Dentistry (B. Evans).
6. Psychiatry (D. Jonas).
7. Neurology (S. Gendelman).
8. Social Services (E. Wincott).
9. Vocational Rehabilitation (F. Marshall).

From the Department of Orthopaedics, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Marion S. Gilbert, M.D., 1100 Park Avenue, New York, N. Y. 10028.

10. Nurse Clinician (J. Best and E. Surgis at CUMC).
11. Data Collector (H. Sarfity).
12. Laboratory Staff (N. Abis).
13. Coordinator (D. Male).

The staff meets each Friday for patient evaluation. After clinic hours, a conference is held to draw up care plans, coordinate care, and make joint decisions on difficult problems. Patient care is rendered throughout the week and reevaluated as decided in the care plan. Once a year patients are brought back for comprehensive reevaluation. Emergency care is rendered through the Emergency Room where there is a special file card listing the patient's diagnosis, infusion record, and known reactions. Many patients are now on a Home Care program and rarely utilized the Emergency Room.

During the past eight years the clinic has functioned on many levels. First and foremost is patient care. Our 100 patients receive primary care while many others have been referred for specialty consultation and surgery. Clinical research projects on product evaluation, inhibitor detection, reconstructive surgery, and adjuvant therapy in oral surgery have been carried out. Education has been stressed on many levels. Fellows, residents, and students rotate through the clinic. Papers by a resident and college student are included in this monograph and represent the contributions made by their special projects. Physicians, nurses and laboratory technicians from foreign countries have spent from one to four weeks in the clinic for specialty training. Conferences on comprehensive care, orthopedic surgery, oral surgery, psychosocial problems and vocational rehabilitation problems have been organized through the clinic. In 1975 the clinic staff was invited to Moscow and Rio de Janeiro to demonstrate comprehensive care. All of the clinic members have participated in patient education programs.

Many similar comprehensive care centers are being set up throughout the country at the present time. Physicians and patients realize that hemophilia is not just a hematologic disorder. This monograph was put together not only to consolidate some of the newer advances in this disorder, but also to help demonstrate one way in which such a clinic can function. Each author will outline his experiences since he or she joined the team. In this way it can serve as a manual for comprehensive care.

Before ending this introduction, I must pay special recognition to those who have made this monograph possible. For years Dr. Martin Rosenthal headed the hemophilia clinic and upheld the tradition of The Mount Sinai Hospital as a hemophilia center. Dr. Henry Jordan struggled with the orthopedic problems prior to the advent of cryoprecipitate. He treated his patients with heavy, bulky braces, but this was the only method he had to prevent bleeding and correct deformity. The untimely deaths of those patients did not allow them to fully appreciate the advances we now take for granted, but the kind and dedicated care is still remembered. These advances could not be put into practice if it were not for the support of Dr. Richard Rosenfield. His contributions to the care of the hemophiliac are too numerous to list. He has supported and cooperated with Dr. Aledort's and my work throughout the years and only with a blood bank of such quality could our clinic continue to function. I personally have to thank Dr. Robert Siffert and Professor Robert Duthie, who have guided me through my training and helped the program with their special skills, and my partners Drs. Sheldon Lichtblau and Burton Berson, who have made it possible for me to spend so much time working with and reaping rewards from the Mount Sinai Hemophilia Team. To those physicians mentioned in this paragraph, this monograph is dedicated.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May-June, 1977
Printed in U.S.A.

Current Therapy for Hemophiliacs: Home Care and Therapeutic Complications*

MARGARET W. HILGARTNER, M.D. AND ELAINE SERGIS, R.N.

Introduction

The introduction of plasma clotting factor concentrates has radically changed the treatment of patients with clotting factor deficiencies in the last ten years, and brought about a remarkable change in the quality of life and probably the longevity for these individuals. The availability of cryoprecipitate and the concentrates of Factors II, VII, VIII, IX and X have made outpatient treatment for bleeding episodes routine, and home infusion or self infusion a possibility for many patients. Hospitalization for inpatient treatment is now rare except for surgical and orthopedic procedures. Early outpatient therapy of bleeding episodes has decreased the number of deformities seen in the past and children born within the last ten years appear to have far fewer deformities. Adjuvant drugs, corticosteroids, and antifibrinolytic agents have been found useful and accepted for hematuria, hemarthrosis, and mouth bleeding. Other antiinflammatory agents, such as Indocin® and Motrin®, are being investigated for chronic arthritis. Aggressive rehabilitation programs and surgical reconstruction have corrected many old deformities. Total comprehensive care of the patient has produced an individual whose quality of life is vastly improved. With this change in life style the patient has changed from a dependent personality to one for whom self-support is expected and feasible. The opportunity for greater self determination in his medical care has come about through self-administration of therapy by the patient or family member.

Current therapeutic management of bleeding episodes in the hemophiliacs will be discussed in this paper with an emphasis on home transfusion. Hemostasis is best achieved by replacement of the missing clotting factor activity. Significant amounts of factor must be given to bring about immediate clot formation and allow regrowth of fibroblasts for adequate healing. The manner in which the clotting factor is delivered will depend primarily on the factor deficiency and the magnitude of the bleeding episode. Other factors, such as age and size of the patient, convenience, acceptability, and cost of product, as well as the method and place of delivery of care to the patient, must be considered. The available products are listed in Table I. Fresh frozen plasma (FFP), is listed as the starting product containing one International Unit of clotting factor activity per milliliter of all the clotting factors, and can

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* Supported by the Children's Blood Foundation.

From the New York Hospital-Cornell Medical Center, Hemophilia Clinic; and the Department of Pediatric Hematology/Oncology, New York, N. Y. 10021.

Requests for reprints should be sent to: Margaret W. Hilgartner, M.D., Hemophilia Clinic, 525 East 68 Street, New York, N. Y. 10021.

TABLE I

Replacement Products 1976

Factor VIII Deficiency	Approx. Units/ml.
Fresh Frozen Plasma	1
Cryoprecipitate	5–10
Concentrates:	
Abbott (Profilate®)	12
Armour (Factorate®)	10
Cutter (Koate®)	25
Hyland (Hemofil®)	25
Parke-Davis (Humafac®)	13–40
von Willebrand's Disease	
Fresh Frozen Plasma	1
Cryoprecipitate	?
Factor IX Deficiency	1
Fresh Frozen Plasma	
Concentrates:	
Cutter (Konyne®)	25
Hyland (Proplex®)	17–18

be used when only small amounts of clotting factor need to be delivered to the patient. Its use is limited by the volume since only 10-15 ml/Kg may be given safely in one dose with an expected rise of 20–30% factor activity. Such levels are insufficient for current surgical practices and accepted medical therapy for patients with Factor VIII or IX deficiencies. FFP is harvested from single-donor units and therefore carries less risk of hepatitis than the pooled concentrates. For this reason it should be considered for those patients with Factor VIII and IX deficiencies who have *mild* disease and are treated infrequently.

Cryoprecipitate, the protein which precipitates in fresh frozen plasma when thawed at 4°C, is rich in Factor VIII and fibrinogen. It is easily prepared in most blood banks capable of component fractionation, and is stored frozen at −20° C (1). Single units can concentrate the Factor VIII approximately 10-fold in 10cc of plasma and 30-60% of the Factor VIII can be recovered from the donor plasma. It also carries less hepatitis risk as a single-donor component. Great variability exists in the product, however, because of twenty-one steps in its recovery process which may affect the yield, and exact dosage calculation may be difficult. (2). However, administration of this small volume, by syringe or drip, decreases the possibility of circulatory overload while providing greater amount of therapeutic material. The cost of this product also varies throughout the country and in some areas may be considerably less than the dried concentrates.

Concentrates of the clotting factor proteins have many advantages and are becoming widely available. Those concentrates available in the United States are listed in Table II and similar products are available abroad. These lyophilized concentrates are made from pooled plasma obtained by plasmaphoresis or as part of a blood bank's program of total donor unit fractionation. The Factor VIII concentrates are prepared from cryoprecipitates and purified

TABLE II

Replacement Products

	Therapeutic Modality	Approximate units/ml.
Factor I	Fresh Frozen Plasma	200–400 mg.
	Cryoprecipitate	20–30 mg.
	Concentrates	1–22 mg.
Factor II	Fresh Frozen Plasma	.75–1 units
	Concentrates: Prothrombin complex:	
	Cutter (Konyne®)	25
	Hyland (Proplex®)	7
Factor V	Fresh Frozen Plasma	0.25–0.50
Factor VII	Fresh Frozen Plasma	1
	Concentrates: Prothrombin complex:	
	Cutter (Konyne®)	38
	Hyland (Proplex®)	40–110
Factor VIII	Fresh Frozen Plasma	1
	Cryoprecipitate	5–10
	Concentrates:	
	Abbott (Profilate®)	12
	Armour (Factorate®)	10
	Cutter (Koate®)	25
	Hyland (Hemofil®)	25
	Parke-Davis (Humafac®)	13–40
	New York Blood Center (Lyoc®)	6
Von Willebrand's	Fresh Frozen Plasma	1
	Cryoprecipitate	
Factor IX	Fresh Frozen Plasma	1
	Concentrates: Prothrombin complex:	
	Cutter (Konyne®)	25
	Hyland (Proplex®)	17–18
Factor X	Fresh Frozen Plasma	1
	Concentrates: Prothrombin complex:	
	Cutter (Konyne®)	31
	Hyland (Proplex®)	14–17
Factor XI	Fresh Frozen Plasma	1
Factor XII	Fresh Frozen Plasma	
Factor XIII	Fresh Frozen Plasma	
Fletcher	Fresh Frozen Plasma	
Fitzgerald	Fresh Frozen Plasma	

further by a variety of methods with some removal of fibrinogen. They can be stored at 4°C in a refrigerator and reconstituted with sterile water, warmed to body temperature, drawn up into a syringe through a filter needle, and infused slowly by syringe. Those more highly purified concentrates with low fibrinogen concentrations are extremely desirable at the time of a surgical procedure or for a patient on high dose therapy for an extended period. The in vivo half-life of fibrinogen is longer than Factor VIII; therefore, concentrates with a high fibrinogen content are less desirable because of the side effects of hyperfibrinogenemia when patients are maintained at high Factor VIII plasma levels for extended periods. The amount of clotting activity is stated on the bottle label and facilitates dosage calculations. Transfusion reactions are virtually eliminated with the removal of white cells and platelets. Occasional problems continue to be seen with cryoprecipitate (3). The convenience of storage, safety and ease of administration, and the standardization of product have made these concentrates highly acceptable both to physician and patient.

Disadvantages arise from the pooling of the starting plasma. Hepatitis continues to be a problem although all products and most donors are now tested by third-generation tests, usually radioimmunoassay, for the Hepatitis B surface antigen (HB_sAG). Some 60–80% of infected plasma is detected. However, 20-40% is not, nor are those infected with the other viral agents which may cause hepatitis, e.g., Hepatitis A, E or "non A - B." Another disadvantage may arise with significant titers of A and B isoagglutinations that may cause hemolytic anemia in a patient with red cell type A, B or AB. A final disadvantage is the cost of the manufacturing procedure that is closely tied to the cost and availability of plasma. Currently the prices of concentrates are the same as cryo but such may not always be true, and cost may be an important consideration in the choice of product for therapy.

The lyophilized concentrates of Factors II, VII, IX and X (Prothrombin complex) are marketed primarily for treatment of Factor IX deficiency but can be used for bleeding episodes in patients with acquired or congenital deficiencies of Factors II, VII, IX and X. The relative amounts of the individual factors found in these concentrates are listed in Table II. Again the advantages of these concentrates include standardization, storage at 4°C, easy reconstitution with sterile water and ease of administration with syringe. The disadvantages include a greater concentration of the hepatitis antigen (Hb_sAG) than that found in Factor VIII products with a concomitantly higher incidence of hepatitis associated with their use and increased amounts of thrombogenic material. Although the manufacturing procedures are different for the two products available in the United States, these products and those made with the same procedure in other parts of the world contain variable amounts of activated Factors, IXa and Xa. It has been suggested therefore that these products be administered with great caution in those patients with preexisting liver disease or vascular disease and according to the recommendations of the International Task Force (4).

Whole blood is not a product of choice for any hemophilic bleeding episode and unnecessary for anemia. Packed red cells are the product of choice for anemia.

Calculation for Replacement Therapy

Dosage to replace a factor deficiency is calculated on the basis of the patient's weight, assumed plasma volume and the severity of the bleeding episode. It is convenient to consider the administration of clotting factor in terms of International Units per measure of body weight. By definition, 1 International Unit of Factor VIII or IX is that amount of clotting activity found in 1 ml of fresh normal pooled plasma and 1 International Unit is equal to 100 percent clotting factor activity. For simplified calculations and assuming equilibration with the extracellular fluid, 1 unit of Factor VIII per Kilogram of body weight will raise the patient's plasma level 2% and 1 unit of Factor IX per Kilogram of body weight will raise the patient's plasma level 1%. The difference in plasma level attained is related to the greater amount of Factor IX which goes into the extravascular space and may be related to molecular size.

Subsequent dosage is based on the desired plasma level, severity of the bleeding episode, and utilization of the infused factor, the half disappearance time and biological half disappearance time of the infused factor as well as the length of time desired for replacement therapy.

Previous work has shown that 20% of Factors VIII and IX are necessary for hemostasis when therapy is given in a single infusion. Abildgaard (5) states that for control of acute hemarthrosis, a plasma level of 40-50% will achieve hemostasis and allowing for natural decay will still provide replacement coverage for at least 24 hours. This can be given as outpatient therapy and repeated in 48 hours if bleeding is not controlled. Such therapy is adequate for large bleeding episodes, particularly if the episode has progressed for 6-8 hours before therapy is given. Our own experience and that of others where therapy is given within 4 hours of onset of a bleeding episode on a home care program suggests that one-half to one-third this amount of therapy may be sufficient for good healing. Adjuvant measures such as ice and ace bandages are quite useful. Immobilization of a weight-bearing joint for 24 hours is occasionally necessary. When the lyophilized products are used, dosage may be calculated to the nearest vial, using the assay amount printed on the manufacturer's label. When bags of cryoprecipitate are used, calculations again should be to the nearest bag and should probably be calculated using 60 units per bag as the average content. This amount of course varies from blood bank to blood bank.

Treatment Regimens

It is difficult to be absolute about therapy regimens because of the variability of the disease in the patient, the severity of the bleeding episode, and the state of the tissue area in which the bleeding episodes occur. There is considerable difference of opinion throughout the world concerning the amounts of replacement material that should be used and the dosage levels that should be maintained. The cost and availability of materials are frequently a determining factor in therapy. The regimen given here has been derived through education and experience. Therapy for many bleeding episodes may be one-third to one-half conventional dosage if given within 4 hours of onset. This experience has been noted by many clinics for patients on Home Care Therapy programs.

Hematoma, or hemorrhages under the skin and within muscles can frequently be controlled by ace bandages, pressure, and ice. Those which cannot be controlled easily within a few hours may cause muscle contraction and require replacement therapy. Bleeding in certain muscle groups such as those in the posterior leg, the soleus and gastrocnemius, should be treated early to avoid contraction and scarring that are difficult to rehabilitate. When replacement therapy is necessary, 10-20 units per Kilogram given once suffice both for hemophilia A and B. Hemophilia B frequently can be treated with the lower amount, and FFP may be sufficient to deliver this small amount. Patients with von Willebrand's disease usually can be treated as mild hemophiliacs with the lesser amount of concentrate. These are considered minor bleeding episodes and are relatively easily controlled.

Hematuria due to a bleeding diathesis is usually renal in origin and must be differentiated from nephritis. Although disconcerting to the patient, it is rarely the cause of severe difficulty. Pain in the flank area often accompanies clotting in the renal pelvis and signifies cessation of gross hematuria. Current treatment includes steroids and factor replacement. Abildgaard et al (6) reported the effectiveness of short term steroids given for 48 hours at the onset of hematuria. If this is unsuccessful, replacement therapy should be given. Amicar® (EACA) is contraindicated because of protracted renal dysfunction which follows clot formation with EACA on the fibrinogen strands and subsequent lack of clot lysis. Hematuria without trauma is uncommon in other than congenital deficiencies of Factor VIII and IX. Admission for replacement therapy may be necessary.

Hemarthrosis, spontaneous bleeding into the joints, occurs only in the severe hemophiliacs (Factors VIII and IX) and almost never in von Willebrand's disease. Trauma may be followed by hemarthrosis in all grades of the disease, the milder forms as well as in the deficiencies of Factors X and XI. When synovial changes appear, bleeding may occur without provocation. Replacement therapy should be 20-30 units per Kilogram body weight. Repeat doses may be necessary in 24-48 hours if the bleeding is severe or the joint has a chronic arthropathy. However, repeat doses are usually not necessary and the need for repeated doses should alert the physician to other problems. Dosage should be examined and efficacy of material or the onset of an inhibitor should be suspected. Bleeding into the elbows and wrists usually may be considered minor bleeding episodes and may be treated with smaller amounts of concentrate than when the weight-bearing joints, ankles, knees, and hips are involved. The latter should always be considered as major bleeding episodes and treated with the larger amounts of concentrate. Steroids have been advocated by Kisker et al (7) as well as the author at 1-2 mg per Kilogram up to 60 mg for three days as an inflammatory agent to be used with the replacement therapy at the onset of a hemarthrosis. Its major effect seems to be in those joints where synovial hypertrophy and synovitis have developed. Shoulder bleeding is rare without provocation and should be treated as a major bleeding episode. Both hip and shoulder hemarthrosis may be deceiving because of the size of the joint into which several hundred mililiters may be lost symptoms are apparent.

Adjuvant therapy. Ice and ace bandages are often helpful for hemarthrosis. Additional support to the ankles may be given with firm high-laced boots. Should a bleeding episode progress sufficiently to cause severe distention of the joint, making the overlying skin tense and shiny, aspiration of the blood may be necessary. Replacement therapy should be given just before the procedure and a firm ace bandage applied afterwards. Some orthopedists advocate aspiration for all large hemorrhages but with the institution of replacement therapy within 4-8 hours after the onset of bleeding, this procedure is usually not necessary.

Peripheral Nerve Bleeding. This is not uncommon in severe hemophiliacs. It is difficult to diagnose and extremely painful. External swelling or tenderness are not seen. Signs of nerve pressure and irritation such as numbness, tingling, and paresis may be the only objective findings. Pain may persist in the face of adequate replacement therapy of 20-30 units per Kilogram given daily for a week or more and paresis for up to 6 months. In the interim, flaccid muscles should be given electrical stimulation and passive exercises to maintain muscle tone. Femoral nerve palsies and ulnar palsies are the most common. The subject is treated in greater detail in another paper.*

The Hazardous Bleeding Areas, central nervous system, retropharyngeal, and retroperitoneal, are the only bleeding sites requiring mandatory admission for observation and therapy. The first two may be lethal if not treated adequately, as may the third, but less rapidly. Any head injury should be treated as a potential bleeding episode and treated accordingly with the extent of therapy dependent on the severity of the injury and the objective findings. A severe headache should be suspect as a CNS bleeding episode. Such spontaneous episodes are more common in patients with Hemophilia B and rarely occur without trauma in the other deficiencies. Plasma levels should be maintained in the normal range with 40-50 units per Kilogram for three days.

Retropharyngeal bleeding frequently accompanies a pharyngitis and should be suspected when a patient complains that he cannot swallow his saliva. With such a complaint, a lateral x-ray of the neck will help to determine the presence of a retropharyngeal mass and the extent of airway obstruction. With adequate replacement therapy of 40 units per Kilogram every 12 hours for three doses, tracheostomy should not be necessary.

Retroperitoneal bleeding presents as lower abdominal pain and iliopsoas muscle irritation and/or contraction. On the right side this may be mistaken for appendicitis. Therefore, a dose of replacement material of 40 units per Kilogram should always be given before calling the surgeon. Plasma levels should be maintained in the normal range for three or four days. Should any of these bleeding manifestations require operative intervention, the surgeon should be reassured that hemostasis will be as good as in a "normal" patient or one without a known coagulation problem. The surgeon must, however, be meticulous about his technique in clamping and ligating as many small vessels as feasible. Clamping and cutting between the clamps for delineation of planes is better than blunt dissection, and excessive cautery is unwise.

Elective Surgery is now commonplace for the patient with a congenital or acquired clotting factor deficiency and may be undertaken whenever necessary to provide the best medical care to the patient. Certain mandatory prerequisites must be followed to assure a smooth outcome (Table III). The

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* Arnold, W. A. and Hilgartner, M. W., *In* J Bone Joint Surg 59A:287-305, 1977.

TABLE III

Requirements for Elective Surgery

Prior to Procedure:

1. Complete coagulation work-up
2. Incubated test for inhibitors
3. Calculate needs and stock-pile therapeutic material in hospital
4. Survival study for recovery of half-life of therapeutic material
5. CBC, platelet count, reticulocyte count
6. Red cell type

General Surgical Procedure:

Minor

1. Give dose calculated to bring patient's plasma level to 100% one hour prior to procedure (50 units/Kg)
2. Maintain plasma level above 60% × 4 days
3. Maintain plasma level above 20% × subsequent 4 days
4. Assay daily prior to dose

Major

1. Give dose calculated to bring patient's plasma level to 100% one hour prior to procedure (50 units/Kg)
2. Maintain plasma level above 60% × 4 days
3. Maintain plasma level above 40% × subsequent 4 days or until all drains and sutures are removed
4. Assay daily prior to dose

laboratory tests listed will assure confirmation of the clotting deficiency and of the presence of adequate amounts of all the clotting factors necessary for hemostasis. An incubated test for inhibitor is necessary to detect a low titre inhibitor whose anamnestic response might create a postsurgical hazard. The presence of such an antibody is a contraindication to an elective procedure.

Although Table II has been divided into major and minor procedures, it is more accurate to say that a surgical procedure is never minor in a hemophiliac and should not be undertaken lightly. The differentiation of the groups lies in the extent of replacement material necessary for fibroblast growth and good scar formation. Orthopedic procedures require more replacement when raw bone surfaces must heal or when a small amount of postoperative bleeding cannot be tolerated. For example: a small amount of bleeding into or around a prosthetic knee or hip invariably leads to infection and destruction of the surrounding tissues. On the other hand, when an extremity or operative site is held firm in plaster, or when good surgical apposition of tissues can be achieved with sutures, less extensive therapy is required. However, when suturing is required on a laceration, although the procedure is a minor surgical procedure, hemostasis must be controlled in the same manner. Dosages are given broadly and can only be maintained with the assistance of good coagulation laboratory support and daily assays of the patient's plasma.

Adjuvant Drug Therapy

Analgesics. Analgesics have always been an important part of therapy for all hemophiliacs and, although not as important now that early transfusions are advocated, it is imperative that the physician know the effect of these drugs on the clotting mechanism, for it is not in the patient's best interest to produce a secondary bleeding diathesis.

There is an ever increasing list of analgesics containing aspirin and antihistamines which are known to inhibit platelet aggregation and prolong the bleeding time. Patients should be cautioned against the use of any medication containing aspirin compound and several other drugs as listed in Table IV. Propoxyphene (Darvon®), acetaminophen (Tylenol®), and Talwin®, codeine, or methadone may be used as alternatives.

Antiinflammatory Agents. The most widely used and best of the antiinflammatory drugs are the corticosteroids. They have been used in the dose of 1-2 mg/Kg/day for hematuria for 48 hours, acute hemarthrosis for three days and chronic synovitis for 1–3 weeks, as already mentioned, with a maximum dose of 60 mg /Kg/day. Side effects have not been noted for these short courses of therapy. Indomethicin (Indocin®) or phenylbutazone (Butazolidine®), although excellent drugs for arthritic pain, are potentially harmful for the hemophiliac because of inhibition of platelet function caused by these agents and should be used only with caution. Motrin®, the newest of the drugs used by the rheumatologist for arthritis pain, is a known prostoglandin inhibitor with potential in vitro effect, but the in vivo effect is as yet unknown.

Antifibrinolytic Agents. Epsilon-amino-caproic acid (EACA [Amicar®]) and Transexamic acid (Cyklokapron [AMCHA®]) are antifibrinolytic agents that have been used in large scale trials to prevent spontaneous bleeding and for dental extractions both in Europe and in this country. The results have been singularly unimpressive when EACA was used to prevent joint hemor-

TABLE IV

Drug Therapy for the Hemophiliac

Not Recommended		Recommended
Analgesics		*Nonnarcotic agents*
Aspirin		Tylenol Tempra } (acetominophen)
Aspirin-Containing	Compounds	
Bufferin	Empirin	Darvon (plain) (propoxyphene)
Anacin	Percodan	Talwin (pentazocine)
AlkaSeltzer	APC tablets	
Darvon Compound	Excedrin	
Antihistamines		*Narcotic agents*
Periactin (cyproheptadine		Codeine (codeine)
Chlor-trimeton (chlorpheniramine)		Demerol (meperidine)
		Morphine (morphine sulphate)
		Methadone (methadone hydrochloride)
Cough Syrup		
Robitussin (glycerol guaiacholate)		
Antiinflammatory agents		
Butazolidine (phenylbutazone)		
Indocin (indomethacin)		
Motrin (ibuprofen)		

This table lists examples of commonly used drugs, showing those not recommended and those recommended for the hemophiliac.

rhages, but promising when used for dental extractions and other mouth bleeding episodes. A recent study by Ransford (8) claims a significant reduction in spontaneous bleeding episodes with the use of Transexamic acid. The specific prevention of hemarthrosis is not well substantiated.

EACA has not been advocated in the treatment of hemarthrosis since a clot formed with EACA adsorbed to the fibrin strands may not dissolve for many months and may contribute to fibrosis and further joint destruction. It has, however, been used with Trasylol, another antifibrinolytic drug, at the time of synovectomy by Storti et al (9) with 24 hours of replacement therapy. Although they report 66% of their patients have decreased hemarthrosis, 42% have no improvement or decreased joint function. Intraarticular fibrosis due to EACA may contribute to this poor result. However, control studies have not been carried out either to support or discredit this use of EACA.

Home Care

The methods by which these therapies are given have changed radically in the last ten years. Inpatient therapy is no longer necessary for the majority of bleeding episodes with the exception of bleeding in the hazardous areas such as central nervous system, retropharyngeal and retroperitoneal. All other bleeding episodes may be treated in an outpatient facility, or, for those patient/family units who qualify for self transfusion, in a Home Care Program.

Home Care Programs in which patients or their family members transfused replacement factors away from the hospital was first introduced by Rabiner et al in 1965. Other programs developed in the larger treatment centers with guidelines established by the National Hemophilia Foundation, who recognized the value of home therapy but also cautioned that home therapy could not replace comprehensive care. Current standards for a home care program, therefore, consider home transfusion therapy to be one mode of delivery of replacement therapy within a comprehensive care program. The following criteria have been established by the NHF for a home transfusion program and have been the guidelines for the Home Care Program of the CUMC-MSSM program:

1. The patient and his family must be carefully screened for the psychiatric disease which might interfere with judgment or alter the manner in which therapy would be given.
2. The patient and his family should be thoroughly schooled about hemophilia, the types of bleeding episodes, the replacement therapy, and the occasions in which medical attention in a hospital by an M.D. is essential.
3. The patient and his family must be carefully educated in the technology and hazards of the home transfusion program.
4. Only patients over four years of age, with laboratory-proven hemophilia without circulating anticoagulants should be admitted to the program.
5. Record-keeping is essential. A log must be kept detailing the site of bleeding and the therapy given.

6. Routine follow-up examinations must be made every six to 12 months.

The design of our program is as follows:

When a patient expresses an interest in joining the program, or a local physician wishes his patient to go on the program, certain standards must be met. The CUMC patients are screened by a psychologist and physician; the MSSM patients are screened by the psychiatrist and discussed at length by the team for fitness to enter the program. Stability within the family unit, emotional maturity in the patients, and willingness on the part of the patient to assume part of the responsibility of his medical care are some of the factors explored. Those patients with impaired judgment are automatically disqualified. Such conditions as mental retardation, active psychoses, alcoholism, severe depression and drug addiction are contraindications. When a patient or family is found acceptable, they are referred for instruction. Patients are not pressured into the program since unconscious self-assessment appears to be a valuable screening method for fitness in this program.

A nurse practitioner in the Pediatric Hematology division gives the instruction on an individual basis to patient or family member. The time required to develop proficiency varies with each patient from one session of $1^1/_2$ hours to twelve sessions. The level of anxiety in the patient appears to be the determining factor. The transfusionist is taught sterile venipuncture technique, safety precautions for intravenous therapy, and the use of all the replacement materials for the specific type of hemophilia. We prefer the dried products because of stability of material, known potency, and ease of use. However, we recognize the additional cost of these products in some areas of the country and therefore instruct in the use of cryoprecipitate as well. The transfusionist must demonstrate competency in infusion before the patient becomes part of the Home Care Program. At the time of these sessions the patient's knowledge and recognition of bleeding episodes is reviewed. Patients are also instructed in the philosophy of home care treatment which may be quite different from past views of treatment. The current philosophy proposes treatment as soon as the patient believes bleeding has begun, i.e., when the prodromal stiffness or "peculiar" feeling begins in a muscle or joint—or "when in doubt, treat." Patients are instructed to transfuse as soon as possible for routine bleeding episodes, within 4 hours of onset. Smaller amounts of replacement material are sufficient for hemostasis when bleeding is not allowed to progress. In our program the patient during the first year in the program must contact the doctor on call prior to a transfusion to discuss the episode and the therapy to be given. Thereafter, they may follow a therapy dosage schedule tailored for each type of bleeding episode and call into the Center at the beginning of the next working day. The therapy schedule also indicates when a physician must be called or seen for serious bleeding episodes.

A few very serious bleeders, those who bleed more than once per week, have been placed on a prophylactic program of 2 or 3 tranfusions per week. Short-term prophylaxis may be used at the time of reconstructive surgery, intensive physical therapy programs, or to allow a progressive synovitis to heal.

The bleeding log, which details the site of bleeding, the amount of therapy given, and the details of the transfusion itself, is kept by the patient and sent to the physician in charge every three months for review. This log must be submitted before additional replacement material can be dispensed. In this way the physician may become aware of a joint that is not healing or is rebleeding frequently because the potency of the material has deteriorated or because of the development of an inhibitor. Early recall for a visit can then be scheduled.

The standard for follow-up care includes the following:

1. Complete physical examination every 3-6 months, depending on the frequency of bleeding episodes.
   At that visit: liver function studies; SGOT, SGPT, alkaline phosphatase, total bilirubin, total protein, A/G and BUN, Hepatitis B antigen and antibody, CBC, urinalysis.
2. Orthopedic examination; yearly assessment of range of motion and radiologic joint survey.
3. Visit with social worker; referral to genetic counselor or vocational rehabilitation counselor if necessary.
4. Review with nurse practitioner.

The results of providing medical care in this manner are short term since most programs have only a three- to four-year followup. Much of the data is anecdotal since "hard data" have yet to be accumulated:

1. Compliance has been 90% in our clinic for patient-physician contact, and 95% for record-keeping. Other clinics with more stringent third-party payment systems report 100% compliance for record-keeping.
2. Failures of the therapy program to impede orthopedic diseases as outlined by Levine (10) and his group could be associated with lack of compliance on the part of 6/72 patients who did not transfuse as often as indicated. Progressive arthropathy occurred in 8/78 (10%) patients followed in our clinic and in 9/72 (12%) followed by Levine in the year 1973. Of our eight patients, five had a grade IV arthropathy at the time of admission to the program which became worse over the next two years; three of the eight have gone from grade I to grade III arthropathy with adequate early therapy of each bleeding episode. These three patients are children whose progressive arthropathy suggests that hemostasis alone is not the universal answer to this sequela. This inflammatory disease within the joint, initiated by bleeding, must have another etiology. The overall figure of 88% maintenance of joint status is a marked improvement over the 88% of patients who developed progressive arthropathy prior to Home Care in Levine's study, as well as our own.
3. School attendance and job absenteeism is the only measure of the patient's function in society at the present time. School attendance of 17 children improved from average 41 days absence to 25 days absence per year with the advent of home care. Job absenteeism of the adult was improved anecdotally but not documented as yet. Other morbidity measures taken from Levine's data includes severe bleeding and delay in

consultation with physician following trauma. Chronic hepatitis has developed in a family member known to our clinic and in one of four families noted by Levine to have accidentally stuck themselves with the needle used by the patient. Damage to veins and sepsis has also occurred from improper handling of the materials.

4. Financial data: Levine has computed the data for his patients during the year 1972 and again in 1973 and found a reduction of 45% in total health care costs to the patient. Costs were reduced from $5,895 in 1971 to $3,209 in 1972 and $3,511 in 1973. The cost and amount of concentrate were approximately the same in the control year and home treatment years. The fall in total cost was due to lack of emergency room fees and physician fees. Third-party coverage has been obtained for 69/72 of his patients. In our own clinic we have third-party coverage of some type (Blue Cross, Crippled Children, Medicare, Medicaid) for all. The change in social and psychological adjustment to the disease remains to be measured. A change in "life style" as evidenced by the amount of traveling at home and abroad, however, gives evidence of the true emancipation of these patients and their families from the hospital environs. College attendance has increased; the number of applicants for full-time employment has increased. The level of anxiety and fear of death seems to have dropped precipitously in our own clinic population.

Therapeutic Side Effects

The total medical problems of the patient with hemophilia has not been completely solved. Advances in the technology of fractionation have brought enormous change in the therapy given to the hemophiliacs which has been superior to previous therapy. However, many side effects occur in multiple systems, caused by agents in the material now being given to these multitransfused patients. These include liver disease, renal disease, inhibitors to the transfused factors, thrombosis, and a secondary bleeding diathesis due to platelet dysfunction.

Transfusion reactions no longer demand the attention previously given to them, but occasionally do occur and are mentioned here as a side effect of therapy. Fever, chills and hives due to white blood cell and platelet contamination of plasma can be seen when fresh frozen plasma is used. Acute pulmonary problems have been reported with the use of cryoprecipitate due to white blood cell antigens (3). These antigens should be removed from the lyophilized products and these problems are not seen with the concentrates. Headache and abdominal pain are directly related to the speed of transfusion and are probably due to the protein load infused. The change in plasma osmolarity induces a vascular fluid expansion responsible for the immediate distress. Slow infusion of concentrate is therefore advocated. Occasionally a patient may have episodes of wheezing, flushing or difficulty in breathing when given concentrate, due to the higher titre isoagglutinins in these products. These titres may vary from lot to lot and do not preclude further use of that specific manufacturer's product.

There are multiple causes of hepatitis, hepatitis A, B, E and the "non A or E" viruses and the cytomegalovirus. Hepatitis B surface antigen is probably the most significant and has been extensively investigated. The rate of exposure to the HB$_s$AG has increased with the introduction of the concentrates of Factor VIII and IX since they are manufactured from pooled plasma. Testing of Donors or product for the HB$_s$AG had not been carried out routinely until 1974, and then only with the counter-electrophoresis method (CEP). The detection of antigenicity has been improved considerably with the use of the radioimmunoassay (RIA) to approximately 60-80% reliability, now mandated by the FDA on all starting products and donors. The possibility of eliminating all posttransfusion hepatitis, however, seems unlikely in the immediate future. Although clinical hepatitis has been reported as surprisingly low in hemophiliacs, anicteric disease and chronic liver disease are prevalent and reported from many countries. A somewhat higher rate of disease has been reported in the United States when concentrate was used as opposed to cryoprecipitate, but not from such countries as France and Greece where the incidence is higher in the general donor population. In our own clinic, where concentrates have been used for 6 years, data collected over a 2-year period revealed chemical liver dysfunction (in 52%) with little overt disease (2%). The significance of this chronic dysfunction, and the extent to which the patient should be treated remains unclear. Inadequate methods of testing for the HB$_s$AG is obvious. Hopefully the RIA may bring about a noticeable difference in the next decade, and that sufficient liver biopsies will be done in the future to clarify the significance of the data.

Thrombotic disease, the antithesis of the bleeding episodes, is not usually a problem with hemophiliacs. However, thrombotic episodes have been reported by Kasper and by many others, occuring most frequently with the use of the prothrombin complex (Factor IX) concentrates in patients with liver dysfunction. These included patients with congenital deficiencies, patients with liver disease and premature infants. The hypercoagulable episodes included peripheral thrombosis, pulmonary emboli and disseminated intravascular coagulation. The clotting episodes appear to be more prevalent with some of the prothrombin complex products as opposed to others. The thrombogenic material is thought to be activated Factors IX and X (IXa and Xa) respectively. Small amounts of heparin have been added to the concentrates to inhibit this thromboplastic activity. The heparin is insufficient to counteract all of the thromboplastic activity and must be increased when the concentrates are given to a patient with liver dysfunction and compromised ability to clear the activated factors. The International Committee on Thrombosis and Hemostasis Task Force, formed to study the Factor IX concentrates, recommends the use of an additional 5 mg of Heparin/ml of concentrate given. They also recognize that the concentrates have been used with success in many patients with the congenital deficiencies both for short- and long-term replacement therapy. This thrombogenic property has, however, been used for hemostasis in the treatment of bleeding episodes in patients with Factor VIII inhibitors and appears very promising as a therapeutic modality.

A second problem of the prothrombin complex concentrates appears to be the increased incidence of hepatitis (HB$_s$AG) associated with their use (12). The data from our own clinic, although small in number, would corroborate this fact with 6/8 HB$_s$AG positive and 2/8 HB$_s$AG. These two patients have chronic cirrhosis by biopsy. The virus has apparently been concentrated with these concentrates to a greater extent than with the Factor VIII concentrates. This is particularly apparent when the separation is by Cohn fractionation rather than precipitation. The use of the prothrombin complex concentrate should be considered unwise for a patient with severe liver disease except under extreme circumstances.

Perhaps the most difficult side effect of treatment is the development of inhibitors. Inhibitors directed against Factor VIII or IX are gamma globulins of the IgG class (13). The correlation with amount of therapy is unknown but probably does exist in some patients, although development early in life has been reported. Therapy is controversial at the present time. All treatment with Factor VIII has been withheld as long as possible in the past. When replacement factor has been given treatment has been directed towards saturation of the antibody with enough material to achieve hemostasis with or without measurable plasma levels of the factor. When such therapy has been unsuccessful, exchange transfusions in combination with infusions of very large amounts of Factor VIII have been used. Recent experimental therapy has involved the use of the Factor IX concentrates where hemostasis has been attributed to the thromboplastic activity of activated Factor IX and X (IXa and Xa). The results are promising but the use of the material remains uncertain (14).

The effect of large volumes of protein load on multiple organs in the body is unknown. Since the kidney is the ultimate filter of proteins, renal dysfunctions secondary to deposition of these proteins in the glomerulus has been postulated (15).

An iatrogenic secondary bleeding diathesis can be produced with the administration of long-term Factor VIII concentrates with high fibrinogen content. Since the T 1/2 of fibrinogen is 80 hours as opposed to the T 1/2 of Factor VIII of 8-12 hours, fibrinogen concentrations will rise in a patient given such therapy over a long period of time. When the plasma fibrinogen rises to 1.5-2 grams% the plasma becomes viscous. The red blood cells become coated and clump, giving the rouleaux formation on smear. Platelets do not adhere or aggregate and an iatrogenic thrombasthenia is produced. This phenomenon was reported by Halvorsen (16) and corroborated in vitro. It is for this reason that the concentrates with low fibrinogen content are used in our clinic for patients requiring more than 8-10 days of replacement therapy and for those receiving high dose prophylactic therapy for rehabilitation or for surgical procedures. Every effort is made to maintain the fibrinogen around 1 gram%.

Finally, mention should be made of the isoimmune hemolytic anemia caused by isoagglutinins concentrated and transfused with the concentrates. This may occur in a patient with blood type A, B, or AB although efforts are made through pooling of all red blood cell types to minimize titre of these naturally occurring antibodies. The Coombs positive hemolytic anemia which may occur is self limited and will disappear as the concentrates are withdrawn. Steroid therapy may be necessary if hemolysis is severe and transfusions required for subsequent anemia.

Summary

The life spans and life styles of the patients with hemophilia have changed radically over the last ten years. The type of medical therapy and the method of delivery of this medical care have changed the outlook for those chronically ill patients. Crippling is less in children and orthopedic deformities do not progress at the same rate in adults. Children have improved school attendance; young men and women may attend college and graduate schools without difficulty. Adults may hold a job without fear of absenteeism. There are fewer dollar costs of the disease for the patient and the psychiatric cost of this chronic illness is markedly less. The quality of life is improved and the patient may develop a new self confidence which allows him to function as a productive member of society. Greater emphasis must now be placed on the investigation of the complications of increasing longevity and the therapeutic materials.

References

1. Pool, J. and Shannon, A. E.: Production of High Potency Concentrates of Antihemophilic Globulin in a Closed-Bag System, New Engl J Med 273:1443–1445, 1965.
2. Pool, J. H.: Cryoprecipitate Quality and Supply, Transfusion 15:(4)305–306, 1975.
3. Reise, E. P. Jr., McCullough, J. J., and Craddock, R. R.: An Adverse Pulmonary Reaction to Cryoprecipitate in a Hemophilic, Transfusion 15:583–588, 1975.
4. Menache, D. and Roberts, H. R.: Summary Report and Recommendations of the Task Force Members and Consultants, Thromb Diath Hemorr 33:645–647, 1975.
5. Abildgaard, C. F.: The Management of Bleeding in Hemophilia, Adv Ped 16:365–390, 1969.
6. Abildgaard, C. F., Sionone, J. V., and Schulman, J: Steroid Treatment of Hemophilic Hematuria, J Ped 66:117–119, 1965.
7. Kisker, C. T. and Burke, C: Double-Blind Studies on the Use of Steroids in the Treatment of Acute Hemarthrosis in Patients with Hemophilia, New Engl J Med 202:639–645, 1970.
8. Ranisford, S. G., Jounar, S. J., and Hall, A: Transexamic Acid in the Control of Spontaneous Bleeding in Severe Hemophilia, Thromb Diath Hemorr 30:272–276, 1973.
9. Storti, E., Traldi, A., Tosati, E., and Jaboli, S. G.: Synovectomy in Hemophilia. A New Therapeutic Approach and Efficient Technique of Hemostasis, Gazzetta Sanitaria 29:11–17, 1970.
10. Levine, P: Efficacy of Self Therapy in Hemophilia, New Engl J Med 29:1381–1884, 1974.
11. Kasper, C. K.: Thromboembolic Complications. Thromb Diath Hemorr 33:642, 1975.
12. Menache, D.: Clinical Use of Factor IX Concentrates, Thrombos Diath Hemorr (Stutgart) 33:597–599, 1975.
13. Shapiro, S. S. and Hultin, M.: Acquired Inhibitors to the Blood Coagulation Factors, Seminars in Thrombosis and Hemostasis 1:336–385, 1975.
14. Abildgaard, C. F. L. Britton, M., and Havison, J.: Use of Prothrombin Complex Concentrate (Konyne) for Treatment of Hemophilias with Factor VIII Inhibitors, J Peds 88(2) 200–206, 1976.
15. Lazerson, J.: Renal Disease in Hemophilia, Prog Ped Hem/Onc 1, 1976 (In press).
16. Halverson, E. P.: Transient Acquired Defect in Platelet Function following Therapy with AHF Concentrate, Annual New York Area Seminar on Hemostasis, February, 1976 (In press).
17. Seeler, R. A. Telisari, M., Langetenning, P., and Ashenhurst, J.: Comparison of Anti-A and Anti-B Titers in Factor VIII and IX Concentrates, J Peds 89(1)87–88, 1976.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May-June, 1977
Printed in U.S.A.

Methods of Care, Products Available, Complications of Therapy

LOUIS M. ALEDORT, M.D.

Methods of Care

Three aspects of methods of care will be discussed; delivery of care, its setting, and the treatment program.

1. Who is Delivering: The recent Booze, Allen, Hamilton study under the auspices of the National Heart and Lung Institute showed that almost 25% of the patients with moderately severe or severe hemophilia are treated by physicians who only have one such patient. Physicians who treat more than several patients with hemophilia and are not part of a hemophilia center are more than likely maintaining familiarity with the field. On the other hand, there are a small number of physicians who are fully committed to the treatment of hemophiliacs on a large scale and are involved in comprehensive care hemophilia centers.

In the United States it is the consensus of providers that the ideal way to deliver hemophilia care is by comprehensive care. This means a coordinated multidiscipline approach in order to rehabilitate patients by optimal utilization of community and health resources. At present we are able to diagnose the disorder early, provide adequate replacement therapy promptly, and potentially lessen the morbidity of this disease. This can best be accomplished with a comprehensive care team. The team can individualize its approach to a given patient, take into consideration family dynamics, severity of involvement, educational and vocational models open to the child. This author firmly believes that comprehensive care is the optimal therapeutic approach for hemophiliacs.

2. Treatment Setting: Until recently hemophiliacs were treated for bleeding episodes either in a physician's office or in the emergency room of a hospital. The problems attendant on this kind of treatment program were multiple. The biggest problem was delay in treatment and dehumanization. There is no question that the chronic disease patient is unappealing in an acute diagnostic and therapeutic setting such as an emergency room. Once evaluated, there was inevitably delay in treatment since products needed to be ordered, delivered, and administered. This delay in treatment, which in itself is poor care, further reinforced the patient's desire not to be treated. This led to a large number of patients who ignored bleeding episodes or treated with local measures, such as ice and analgesics, rather than go through treatment in an emergency facility. Home care treatment has helped

From the Department of Medicine, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

ameliorate many of these problems. Prior to the era of cryoprecipitate, some hemophilia patients were given their plasma infusions at home. This was initiated in Boston by Dr. Ben Alexander and was followed shortly thereafter in Rochester, New York. It was discontinued because of time involved, expense, and potential hazards of transfusion reactions at home. The concept of these programs lay dormant until approximately 10 years ago when it was reinstituted in Texas. In Fort Worth, high titred Factor VIII plasma was used for home transfusion. This was a most popular program and was utilized by a large number of his patients. One patient moved to Chicago and introduced the concept of the program to Michael Reese Hospital. This led to the first serious study of the efficacy of such a program (1). Since that time multiple home treatment programs have been instituted. The concept of home care is basically a simple one. It is essential to recognize that home care or self care is not an appropriate program for everyone and it is by no means total care. It is one aspect of the comprehensive management of patients with this type of disorder, prompt treatment of a bleeding episode, administered either by the patient or a family member. The patient's ability to accept independence from his physician is as important as his ability to learn venipuncture and the mechanics of treatment. The members of the comprehensive care team evaluate the patient and his spouse or family to determine whether or not he is a candidate for home care. Once a patient is eligible, he must go through a training period to learn preservation of veins, and asceptic techniques. In addition he must be able to recognize when further diagnostic and therapeutic intervention are needed. Patient record-keeping is critical for evaluating appropriate use of product. In some programs the patient must justify all product utilization before additional materials are provided. Patients must be seen on a regular basis to insure complete care.

"Home care" has revolutionized the life of the hemophiliac. It is clear from the available data that patients on such programs spend more time at school and/or work, and the costs for care have decreased. Of interest is that this regimen has made no significant change in product utilization (2). Little is known as yet how home care programs alter the medical aspects of this disease. There is some evidence, however, that, despite early treatment, one can still have progressive deterioration of previously involved joints. Whether or not fewer new joints will be affected is unknown. Data collection by cooperative efforts must answer these questions. In Chapel Hill, hemophilic dogs who have been maintained at hemostatic levels of Factor VIII over an indefinite period of time do not develop any of the complications of the disease. Whether early treatment of bleeding can accomplish the same in man remains conjectural. Our hope is that we will find this to be the case.

3. Treatment Programs: Treatment can be given either on an episodic basis, i.e., for bleeding, or prophylactically. Episodic treatment of bleeding is the most common form of treatment. However, some patients treated in this fashion go through periods where they have multiple bleeding episodes despite early adequate treatment. These can occur either secondary to stress, inappropriate use of analgesics, or alterations in physiology. Recognition of increased bleeding should be followed by a change in program from episodic to prophylactic care. The aim of such a program is to provide measurable Factor VIII levels at all times. Ideal prophylaxis, i.e., maintaining the patient at hemostatic levels greater than 30%, has never been tried over long periods of time in the human model. Only a few programs which maintain patients at measurable low Factor VIII levels have been studied. The rationale for this is that patients with factor levels between 2 and 5% bleed less than those with none. However, no universal prophylactic regimen has yet been designed. Patients vary considerably, and there is neither enough product nor financial support to enter a large number of patients into such programs. In addition the long-term effects of chronic transfusions are still unknown.

At present, the bulk of the patients in America and throughout the world are treated episodically. Those on home care usually receive treatment earlier once a bleeding episode begins, and only a small number of patients are on prophylactic programs.

Products Available

The earliest known treatment for hemophila was either immobilization and/or hypnosis. The descriptive passages in *Nicholas and Alexandria* by Robert Massie showed that Rasputin's influence on the hemophilic bleeding of the Czarevitch probably was due to hypnotism. Immobilization and the use of cold packs are still used in many parts of the world where little or no replacement therapy is available. The modern treatment of this disease (for Factor VIII) is either cryoprecipitate, and/or more highly fractionated products. Table I and Table II list the available American products for the treatment of Factor VIII and IX deficiency. Fresh frozen plasma is now rarely used because of the complications of hypervolemia. Factor IX concentrates also contain Factors II, VII, and X as they are the prothrombin complex. Thus they can be used for other factor deficiency states as well as for patients with severe liver disease or coumadin overdose. The half life of Factor IX is approximately 24 hours. The half life of Factor VIII is 12 hours.

Complications of Therapy

With replacement therapy we now have the potential to make our hemophilic patients normal. Since the discovery of cryoprecipitate with the marked reduction in volume and the appearance of multiple fractionated products we are gaining a large experience with multiply transfused patients. Only with time will we begin to see the complications of therapy. For example, multiple liver function abnormalities are being seen. The data for this is just beginning to be collected and it appears that almost 70% of patients with hemophilia have abnormal liver function (elevations of SGOT and SGPT). Only a few patients have had liver biopsies, and cirrhosis has been found in a few cases. In addition splenomegaly is found in 30% of patients (3). The cause for the

TABLE I

Therapeutic Concentrates for the Treatment of Factor VIII Deficiency

Materials	Source	Storage Requirements	Reconstitution	Remarks
Cryoprecipitate made in many blood banks	Fresh frozen plasma	Frozen at −20°C	with 5–10 cc. saline	Factor VIII contents varies from area to area in concentrations and consistency of quality 60–125 units per bag
Antihemophilic Factor (Abbott)	concentrated and lyophilized from pooled cryo units	4°C	with 10–20 cc. sterile H_2O at 37°C	assayed for approximately 250 units per bottle
Humafac (Parke-Davis)	concentrated and lyophilized from pooled cryo units	4°C	with 10–20 cc. sterile H_2O at 37°C	assayed for approximately 250 units per bottle
Lyoc (Greater NY Blood Program)	concentrated and lyophilized from pooled cryo units	4°C	with 20–30 cc. sterile H_2O	125 units per bottle
Hemofil (Hyland)	extracted from multiple units of cryo-purified and concentrated	4°C	with 10–20 cc. sterile H_2O	250 units and 900 units per bottle
Factorate (Armour)	concentrated and purified from cryoprecipitate obtained from pooled plasma	4°C	with 25 ml sterile H_2O	varying between 200–300 units/via Potency on ea bottle
Koate (Cutter)	human plasma	4°C	with 10–20 cc. sterile H_2O at room temperature	250 or 500 units per bottle. Precautions as with other concentrates
ACTIF VIII (Merieux)	concentrated and lyophilized from pooled cryo units	2–8°C	with 50 cc. sterile H_2O	250, 500, and 750 units per bottle

NOTE: One unit of Factor VIII is that amount found in 1 cc. of fresh normal plasma.

TABLE II

Therapeutic Materials Available for the Treatment of Factor IX Deficiency

Materials	Source	Storage Requirements	Reconstitution	Remarks
Fresh frozen plasma	single donor bag of whole blood	frozen at −20°C	thaw at 37°C	220 units of Factor per bag
Konyne (Cutter)	pooled plasma	4°C	with 20 cc sterile H_2O	assay stated on bottle
Proplex (Hyland)	pooled plasma	4°C	with 20 cc sterile H_2O	assay stated on bottle

NOTE: One International unit of Factor IX is that amount found in 1 cc. of fresh plasma.

abnormal liver function remains unclear. Whether it is due to frequent exposure to virus, such as hepatitis, CMV, etc., or to antigen-antibody complex disease remains unclear. However, it is important that we follow these patients for the incidence of liver disease and its etiology so that we can either eliminate it or offer therapy. Unfortunately, there are no good control groups. It is now well known that there are multiple types of hepatitis to which one can be exposed via transfusion. Hepatitis B antigen, i.e., the Australian antigen is frequent in hemophiliacs. However the antibody titre is significantly elevated in a much larger percent of hemophiliacs when tested. The same is true for hepatitis in Factor IX patients both in the United States and abroad. The findings of elevated Australian antibody in a large number of hemophiliacs probably means exposure to hepatitis virus but whether or not this is related to the abnormal liver functions is still unclear.

The incidence of Factor VIII inhibitors ranges from 5% to 20%. Although Factor VIII antibodies are found in other situations such as penicillin allergy, postpartum, de novo in aged people unassociated with disease, or with immunopathies such as myeloma and lupus, the highest incidence of this disease is found in multiply transfused Factor VIII-deficient patients. There appears to be some relationship to the number and amount of transfusions. The antibodies are gammaglobulins which inactivate the factor. It is a classic antigen-antibody reaction and the kinetics vary according to the specific antibody in a given patient (4). The management of inhibitors raises a significant challenge to the clinician. The anamnestic response is variable in many patients. The mainstay of therapy has large quantities of Factor VIII. Animal Factor VIII preparations have been used in patients with inhibitors. The problem attendant on this has been serum sickness and anaphylaxis after 7 days of treatment. Thus it is a limited form of treatment. Immunosuppression for VIII inhibitors appears to be more effective in patients who are not hemophiliacs (5). A new and exciting treatment has been used in this country and is proliferating in cooperative studies at the present time. This is the use either of activated Factor IX prothrombin complex concentrates (6) or regular Factor IX prothrombin complex concentrates (7). The reason for its effectiveness remains obscure. In vivo it can shorten the PTT and stop bleeding. Even minor surgical procedures can be carried out in the patient. It is important to use caution and such treatment should be used only in major centers where patients can be carefully monitored. Surgical intervention in a patient with an inhibitor is still a most hazardous procedure and few patients if any should undergo an elective procedure with even a low-titred inhibitor.

Factor VIII concentrates are derived from large pools of plasma and thus contain anti-A and anti-B antibodies which cannot be totally removed during processing. Despite their low titre, large infusions of Factor VIII can produce hemolysis in patients with A, AB, or B type blood. This does not seem to be true for Factor IX concentrates. Because of the hemolytic potential of concentrates, all patients receiving large amounts of Factor VIII should be studied prospectively for signs of hemolysis—decrease in hemoglobin, elevation of reticulocytes count, decrease in haptoglobin, and a quantitative Coombs test. The development of a positive Coombs test is variable. Hemolysis can be massive, requiring transfusion. It is important to recognize this entity so that the appropriate transfusion can be given. Blood type O should be used. No patient with O type blood has ever had a product-induced hemolytic episode. In all cases of hemolysis the withdrawal of Factor VIII concentrates leads to eventual cessation of hemolysis.

The problem of thrombosis as a complicating side effect of Factor IX treatment has been recognized by many people including the task force members of the International Society of Thrombosis and Hemostasis (8). In the United States, under the auspices of NHLBI and FDA, there was a recent conference dealing with thrombohemorrhagic complications following infusion of Factor IX concentrates. As one can see from these cooperative data, 20 patients out of 188 patients had thrombotic complications for an incidence of 11%. Patients included in those data had either IX deficiency and/or liver disease. Some of these patients underwent surgery. The significant findings mandate further investigation of the thrombotic potential of the various Factor IX products available on the market, and satisfactory in vitro and in vivo tests to predict the hypercoagulability of these products.

Hemophilia treatment programs have offered the patient a potentially normal life. Expensive materials are available to replace their missing factors. The need to support these materials is great and remains unresolved. In addition the recognized complications of therapy may force us back to the drawing boards in order to provide cheaper and safer products. Our job seems clearcut, and the challenge is great.

References

1. Rabiner, S. F. and Telfer, M. C.: Home Transfusion with Hemophilia A, New Engl J Med 283:1011-1015, 1970.
2. Levine, P. H.: Efficacy of Self-Therapy in Hemophilia. A Study of 72 Patients with Hemophilia A and B, N Engl J Med 290:1381-84, 1974.
3. Levine, P. H.: Personal Communication.
4. Shapiro, S. S. and Hultin, M.: Acquired Inhibitors to the Blood Coagulation Factors, Semin Thromb Hemo 1:336-385, 1975.
5. Green, D.: Factor VIII Antibodies: Immuno Suppressive Therapy, Ann NY Acad of Sci 240:389-399, 1975.

6. Kurczynski, E. M. and Penner, J. A.: Activated Prothrombin Concentrate for Patients with Factor VIII Inhibitors, New Engl J Med 291:164–167, 1974.
7. Abilgaard, C. F., Britton, M., and Havison, J.: Use of Prothrombin Complex Concentrate (Konyne) for Treatment of Hemophiliacs with Factor VIII Inhibitors, J Ped 88(2):200–206, 1976.
8. Menache, D. and Roberts, H. R.: Summary Report and Recommendations of the Task Force Members and Consultants, Thromb Diath Haemorrh 33:645–647, 1975.

The Mount Sinai Journal of Medicine
Vol. 44, No. 3, May-June, 1977
Printed in U.S.A.

Musculoskeletal Manifestations of Hemophilia

MARVIN S. GILBERT, M.D.

Introduction

Hemophilia is an old disease first described in ancient Egyptian treatises, the Hebrew Talmud, and mentioned in the writings of early Arabian physicians. However, it was not until the mid-nineteenth century that Volkmann first noted that patients with hemorrhagic disorders bled into their joints. Prior to this the literature reported an increased incidence of joint tuberculosis, gout or rheumatism in patients with hemorrhagic disorders. In 1892 Konig (1) published a paper in which he described the articular changes caused by intraarticular hemorrhage. He attempted surgical correction of the deformities, but unfortunately he was unable surgically to control the hemorrhage and the patients exsanguinated. Unwilling to repeat these mistakes, orthopedists shunned the unfortunate hemophiliac until the 1940's when Henry Jordan tried to control hemorrhage and correct deformity with casts and braces. He first coined the term "hemophilic arthropathy" (2). The next decade saw enormous strides in the hematologic control of hemophilia. The ready availability of cryoprecipitates and concentrates have made possible the orthopaedic care described in the following sections.

Hemophilic Arthropathy

Clinical findings

The joint is the most common site of hemorrhage in the hemophiliac, and the commonly affected articulations in order of decreasing frequency are the knees, elbows, ankles, shoulders and hips. The small joints of the hands and feet are rarely involved, except following trauma, and to my knowledge spinal involvement has never been documented (2).

Before overt signs of intraarticular bleeding are present the patient perceives what has been described as "a painless, but distinct feeling within the joint." If left untreated this is rapidly followed by distension of the joint capsule and muscle spasm. The joint is warm, tender and motion is limited. The tense joint capsule will usually tamponade the bleeding. The blood will then slowly resorb with return to near normal function. However, recurrence is common and repeated hemarthroses result in a severe and characteristic arthropathy. Synovial thickening may be prominent at this early stage, but later in the disease it disappears. The epiphyseal ends of the bones become enlarged and there is muscle atrophy from disuse. The most common deform-

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From the Department of Orthopaedics, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

ity is that of flexion, posterior subluxation, valgus and external rotation (3). Motion is limited but bony ankylosis rarely follows. The patella is frequently deformed and its excursion limited. Crepitus is prominent, but despite all these findings the patient may not experience disabling pain, as would be

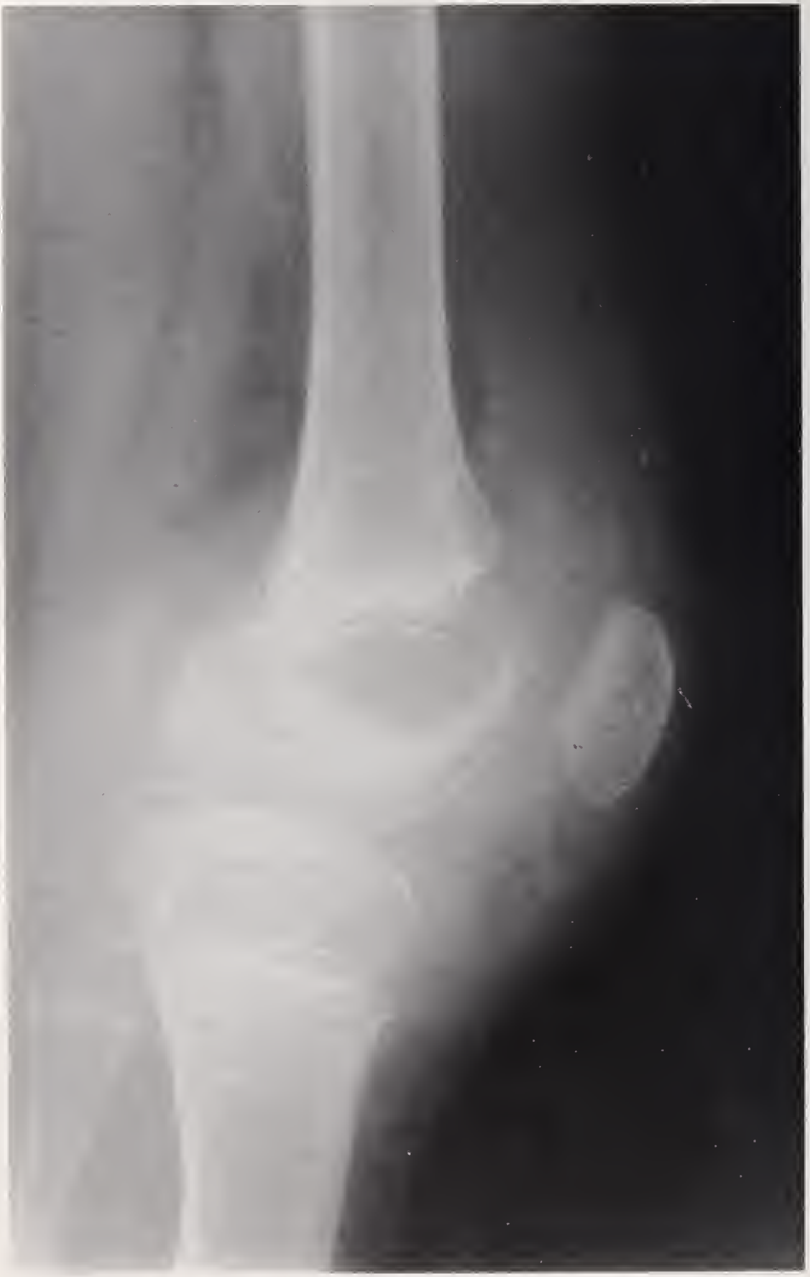

FIG. 1. Joint distension.

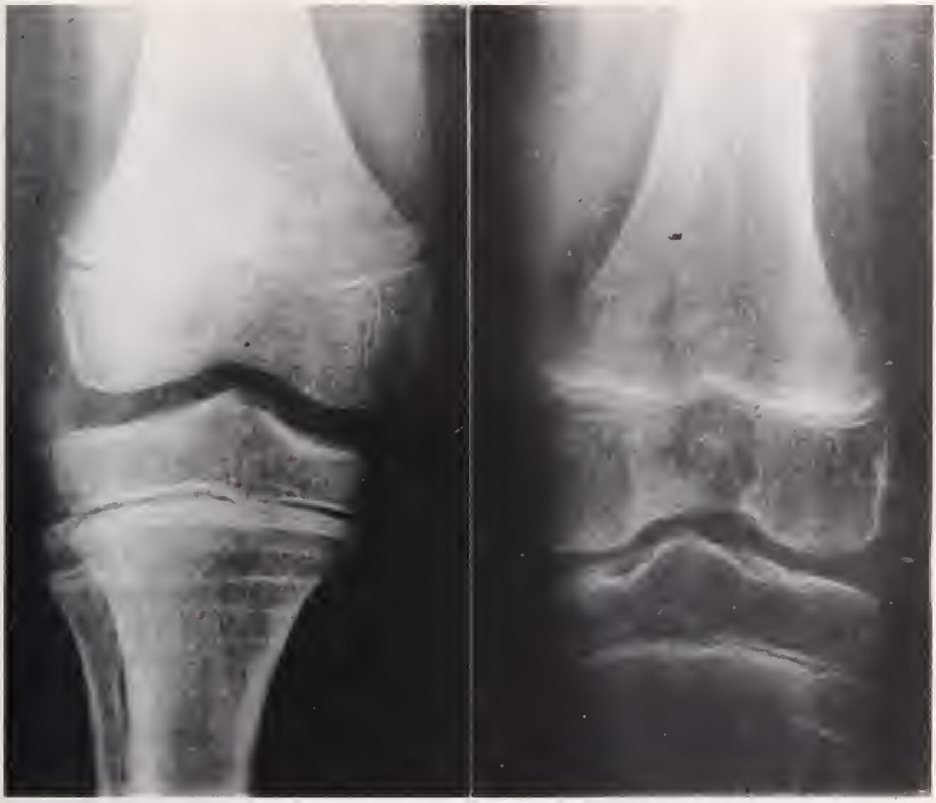

FIG. 2. Epiphyseal overgrowth and osteoporosis.

seen with comparable destruction in other arthritities. It has been postulated that capsular fibrosis results in partial denervation of the joint with a picture similar to that seen in the Charcot joint.

For some unknown reason this picture of recurrent hemarthosis is rarely seen before age 5. At age 7 or 8 the frequency of hemorrhage increases and if untreated the previously described picture evolves. It must be stated at this point that this picture can be eradicated if prompt and adequate treatment is instituted immediately. This point cannot be overemphasized and will be repeated in the section on therapy. However, if treatment is not adequate arthritis will ensue. By the third decade of life the frequency of intraarticular hemorrhage decreases. This has been ascribed to a change in life style and a better understanding of the disease, but also may be due to the replacement of the synovium by fibrous tissue.

Radiologic findings

Several authors (4, 5) have devised classifications for the radiologic changes seen in hemophilia. I have not found them useful because the changes seen are frequently irregular and bizarre. More important is the fact that it is almost impossible to predict the clinical picture from the radiologic findings.

The changes seen in hemophilia are frequently characteristic, but no sign is pathognomonic. Similar changes may be noted in any recurrent arthritis afflicting the growing skeleton.

The changes about the knee will be described in detail and changes unique to other articulations will be described later. The earliest finding is joint space obliteration and distension. This densification is best seen in the suprapatellar pouch on the lateral x-ray and may represent either synovial engorgement or fluid within the joint space (Fig. 1). Osteoporosis, especially at the epiphyseal ends, is noted and has been attributed to disuse and hyperemia. This is frequently seen as a coarsening of the trabecular pattern. Localized hyperemia has been implicated as the cause of condylar overgrowth (Fig. 2). Narrowing of the cartilage joint space and subchondral bone irregularity is then seen (Fig. 3). Progressive cartilage destruction is associated with subchondral cyst formation and areas of bone collapse. In the past it was thought that these cysts were due to intra-osseous hemorrhage, but review of pathologic material tends to discredit this view. In the final stage of destruction there is severe loss of the joont space and mild to moderate osteophyte formation (Fig. 4).

Findings characteristic to the knee are widening and irregularity of the intercondylar notch (Fig. 5) and squaring of the lower pole of the patella (Fig. 6). The former is accentuated, as many of the x-rays are taken in flexion, and has been attributed to hemorrhage at the site of cruciate ligament attachment.

The findings at the elbow are similar, but the irregularity and enlargement of the radial head should be noted (Fig. 7). Advanced destruction may be seen with erosion of the distal humerus into an enlarged olecranon notch. Hip joint hemorrhage in the youth has been followed by changes consistent with avascular necrosis. While characteristic changes may occur at the shoulder, it is not unusual to see large cysts on both sides of the proximal epiphyseal plate of the humerus without articular changes (Fig. 8). Clinically this is usually associated with severe pain and may represent a rare example of intraarticular hemorrhage.

If leg length films are obtained it will be noted that there is increased growth on the side of greatest involvement (6). This stimulation of growth may be due to the local hyperemia. It is frequently missed clinically because of the concomitant flexion contracture.

Pathology and pathophysiology

Knowledge of the pathology and pathophysiology of hemophilic arthropathy is scant but recently investigative work has been stimulated by the availability of cartilage and synovial specimens from reconstructive surgical procedures. The site of primary hemorrhage is the synovium with eventual extension into the joint cavity (7). It has been shown that tissue thromboplastin is absent from synovium as are inhibitors to the fibrinolytic system (8). This may account for the frequency of intrasynovial bleeding. Recurrent hemorrhage results in hypertrophy, hemosiderin deposition, hypervascular-

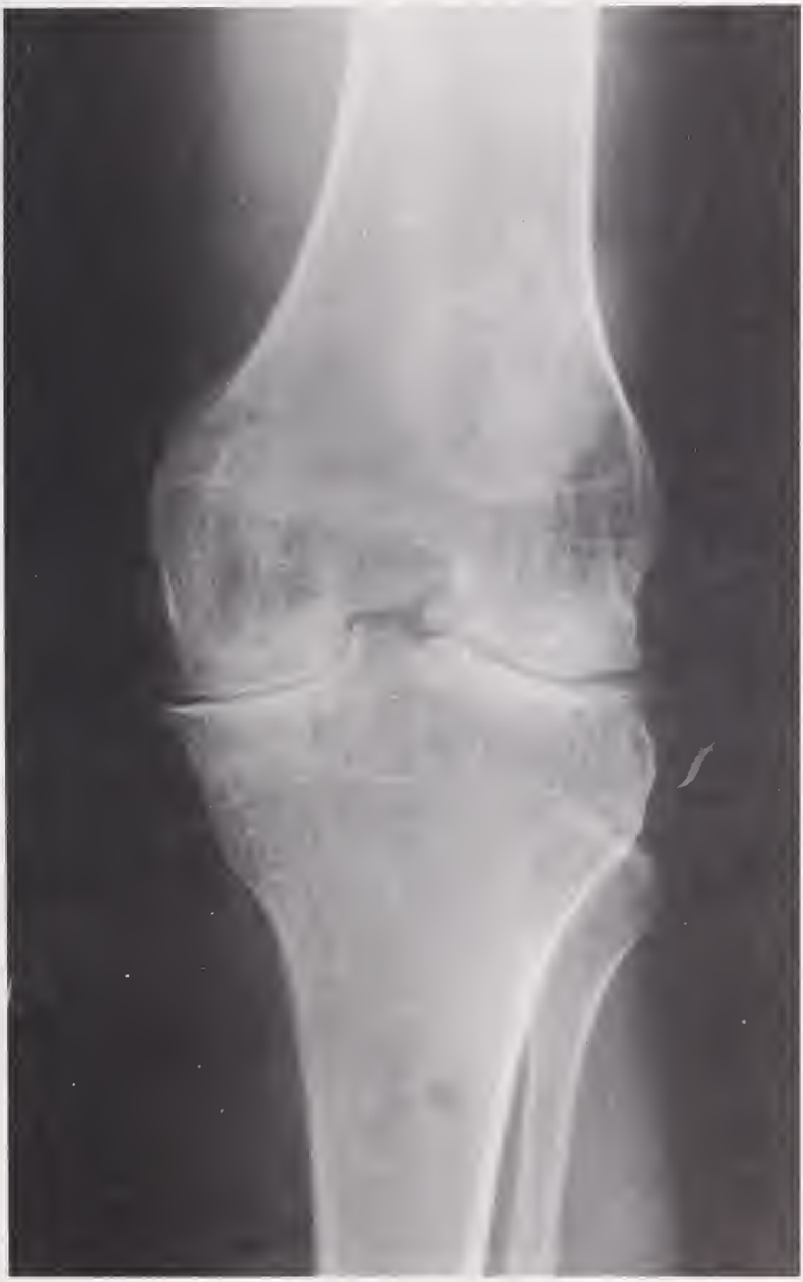

FIG. 3. Joint space narrowing and subchondral irregularity.

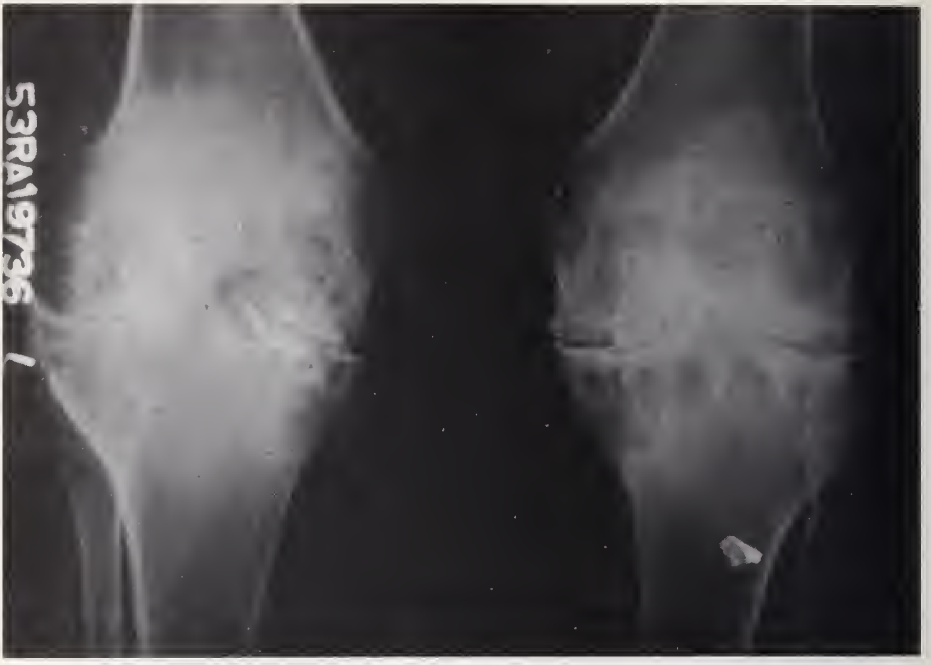

FIG. 4. Advanced changes with cyst and osteophyte formation.

ity, and an inflammatory response (Fig. 9). This predisposes to further hemorrhage. Late in the disease there is extensive replacement of the synovium by fibrous tissue.

Microscopic cartilage destruction begins with fibrillation and metachromatic changes (Fig. 10). Minimal amounts of pannus formation may be noted, and this is followed by erosion and complete destruction. The roles of iron (9), enzymatic destruction (10) and mechanical factors in the destruction of cartilage have yet to be clarified. There is little doubt that both increased intraarticular pressure and the destruction of a firm bony support by cysts, osteoporosis and collapse are important. The levels of acid phosphatase and cathepsin-D are elevated and more closely approximate those of rheumatoid arthritis than osteoarthritis (11). This may simply reflect the inflammatory response and not account for cartilage destruction, but further investigative work is being done.

Treatment of the Acute Hemarthrosis

No joint hemorrhage is so minor that treatment may be deferred or postponed, and no plan of treatment is complete unless it includes replacement of the missing clotting factor to a level sufficiently high to stop the hemorrhage. The level must be maintained long enough to prevent recurrence. Replacement therapy is the mainstay of treatment in hemophilia and must be utilized immediately. Ideally, replacement should begin when the patient notes the previously mentioned prodromal symptoms. Episodes associated

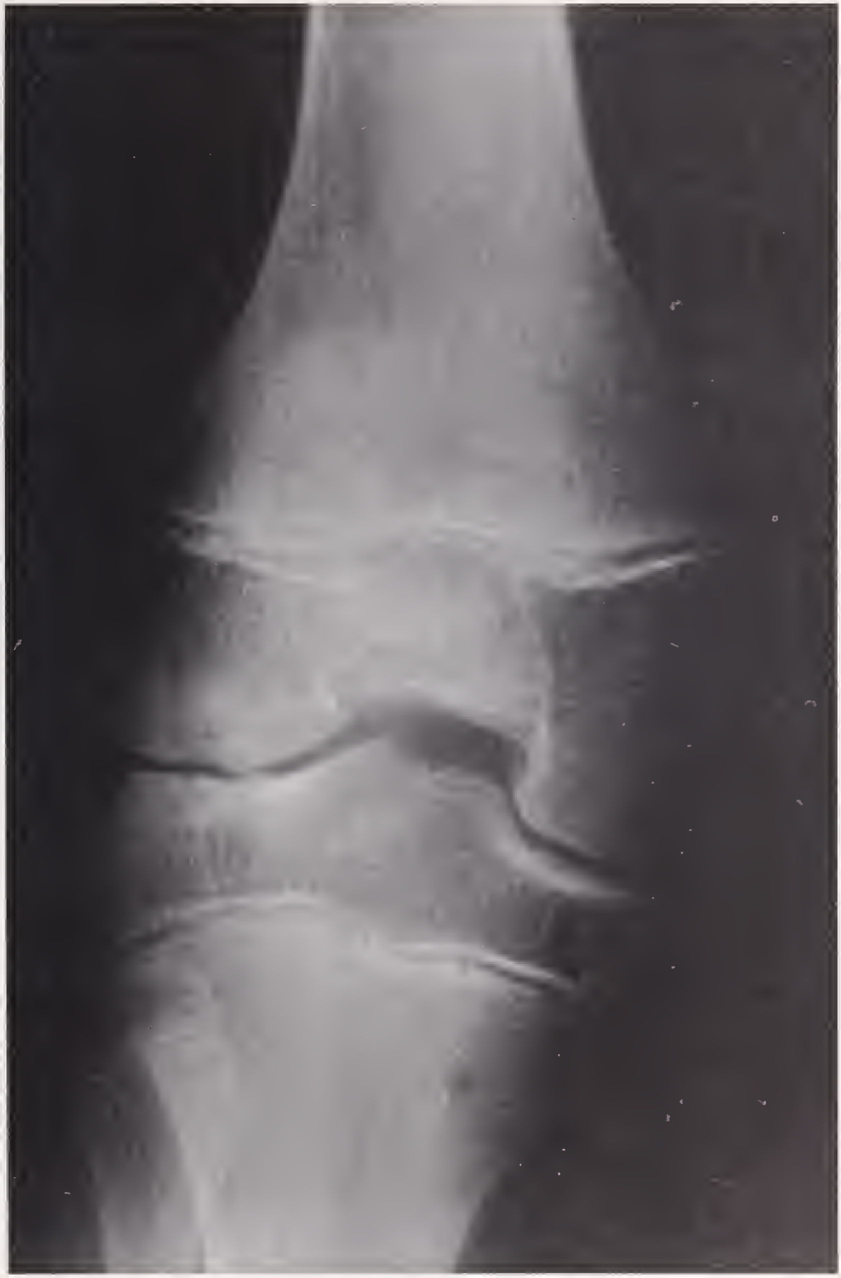

FIG. 5. Intercondylar notch widening and irregularity.

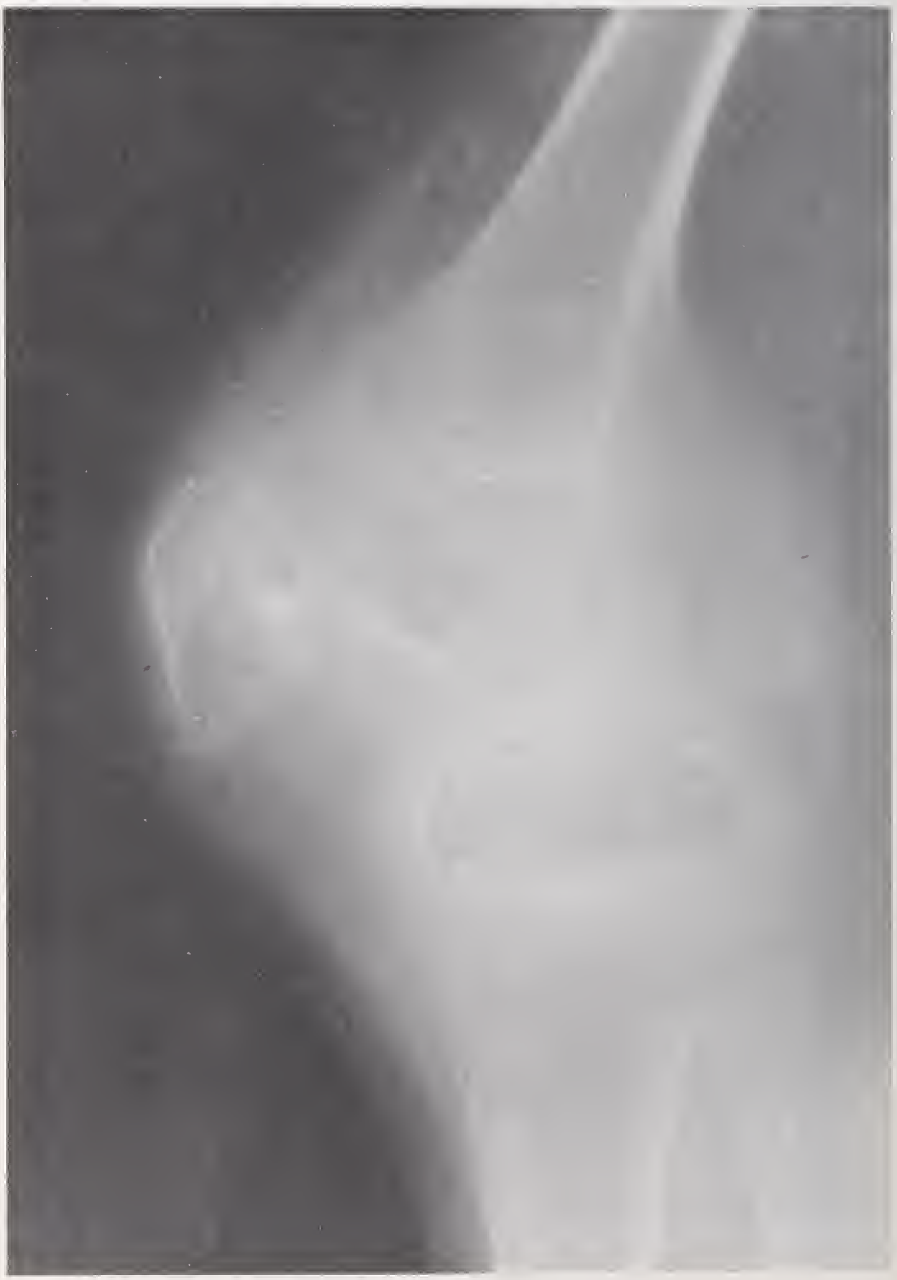

FIG. 6. Square lower pole of patella.

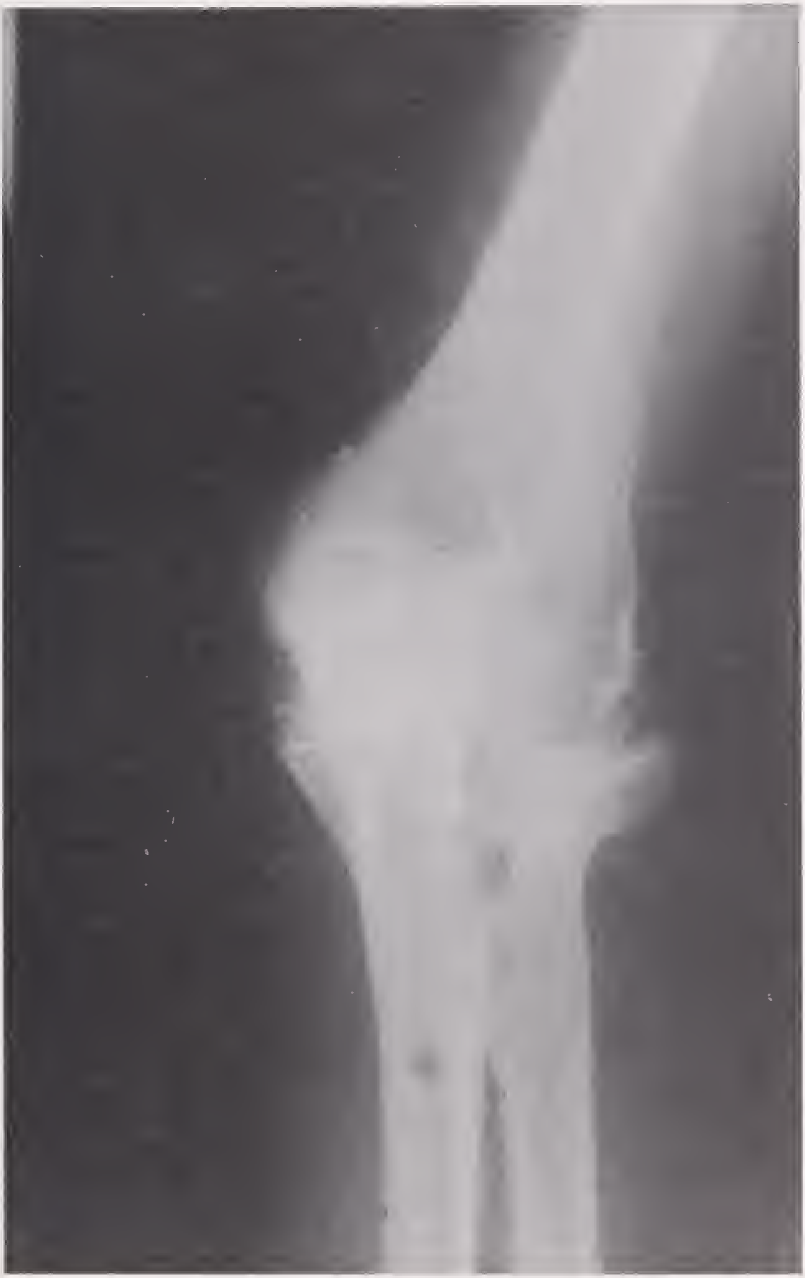

FIG. 7. Elbow with changes demonstrating enlarged radial head.

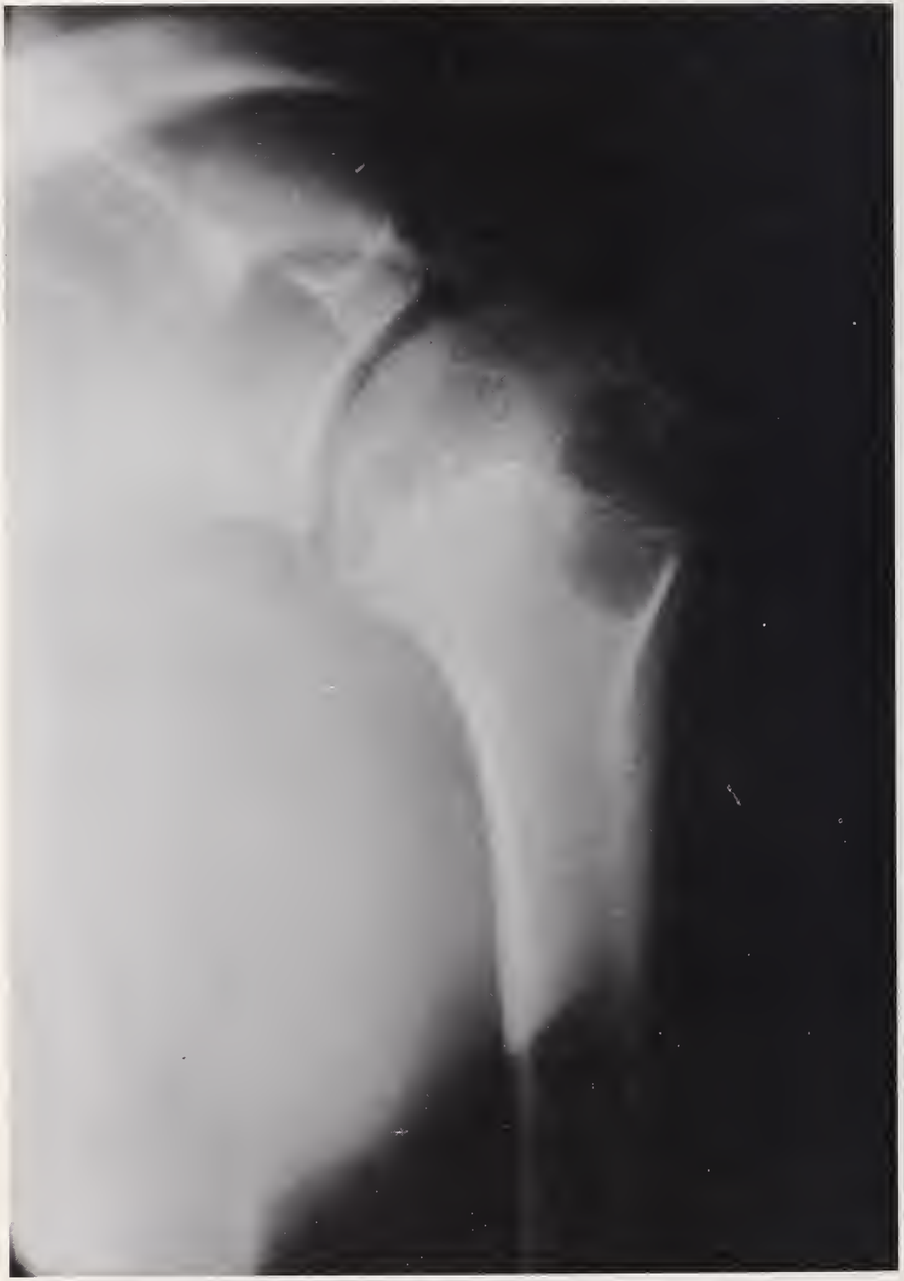

FIG. 8. Proximal humeral cysts without joint changes.

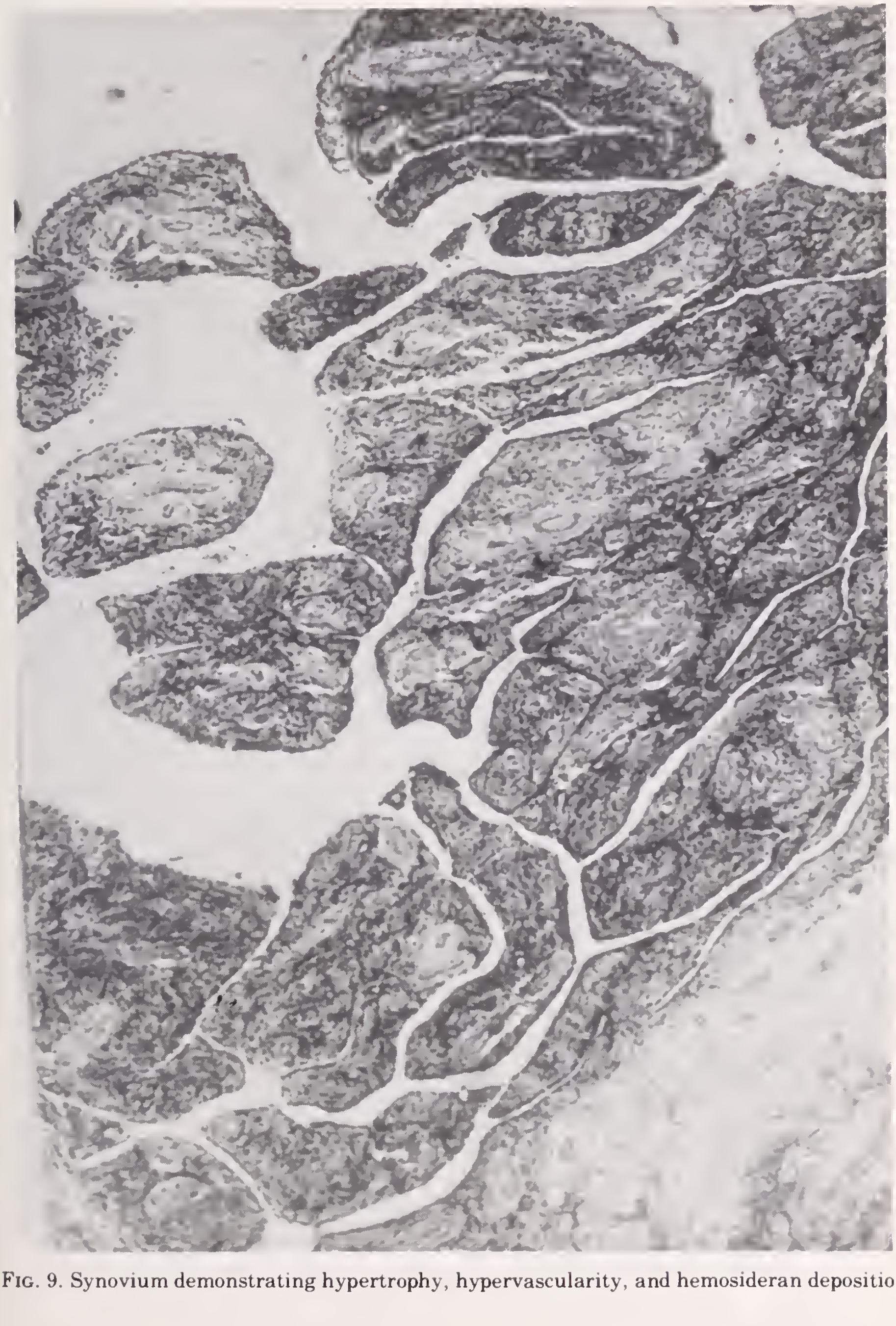

FIG. 9. Synovium demonstrating hypertrophy, hypervascularity, and hemosideran deposition.

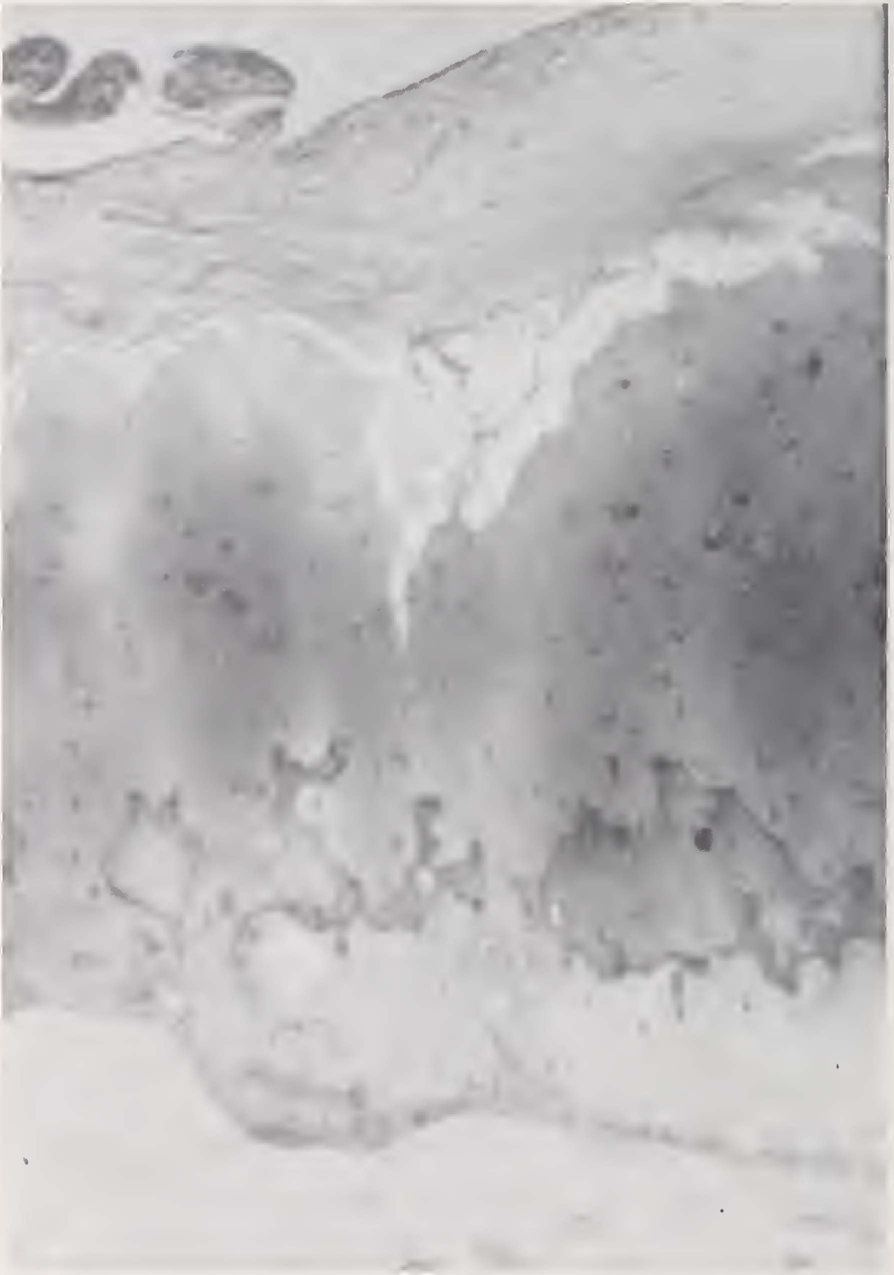

FIG. 10. Cartilage demonstrating metachromatic changes, fibrillation, and pannus overgrowth.

with mild swelling or pain usually respond to a single infusion which achieves a level of 30-40%. If significant swelling or spasm have appeared treatment will be effective but has been started too late. Levels of 50% are usually required and infusion may have to be repeated in 12 to 24 hours. Followup for minor bleeding episodes can be left to the discretion of the intelligent educated patient, but return for physician evaluation is required following the more severe episodes.

Minor hemarthroses may not require immobilization, but some patients find relief from ace bandages, foam rubber splints or slings. The value of ice has been contested, but some patients find that it helps relieve pain and its use is left to the discretion of the patient. Severe hemarthroses in which spasm or flexion is marked should be splinted. At the knee a simple felt Jordan splint may be applied with an ace bandage. This splint may also be purchased with a Velcro™ closure and can be kept at home. For severe deformity a plaster splint is applied in a position of comfort. Attempts at correction should be deferred until bleeding has stopped. Slings and variable angle splints are useful for the elbow. Bed rest is occasionally indicated, but it should only be used during the acute stage and the patient encouraged to return to a functional state as soon as possible.

Aspiration has been advocated at several treatment centers (12). Its value remains unclear and if treatment is instituted quickly it may not be necessary. Indications for aspiration include 1) a tense, painful joint which has not responded within 24 hours to replacement therapy and immobilization; 2) pain which cannot be controlled by analgesics; or 3) evidence of neurovascular or skin compromise. Contraindications to aspiration include the presence of inhibitors, local factors such as open or infected overlying skin or an uncooperative patient or family. Aspiration should be performed simultaneously with replacement therapy. A large bore needle, at least 16 gauge, should be used as small clots frequently will be encountered. Levels of approximately 50% should be achieved and a plaster splint applied. A second infusion 12 to 36 hours later is recommended.

Analgesics can be left to the discretion of the treating physician but obviously any aspirin containing compound is contraindicated because of the potentiation of bleeding. Intramuscular injections should be avoided. The indiscriminate use of narcotics must be avoided because of the chronic nature of the disease, but frequently the pain is severe and their use necessary.

Oral steroids have been shown to decrease some of the associated inflammatory processes and are used at many centers (13). Their side effects are well known, but few problems are encountered if they are used in a short regimen such as Prednisone 1 to 2 mg per Kg per day for three to four days. Other antiinflammatory medications such as indeomethazone and phenylbutazone should not be used because of their inhibition of platelet function. Muscle relaxants and sedatives may occasionally be useful.

Joint rehabilitation must be started as soon as possible. Isometric exercises may be started immediately and as soon as the acute symptoms recede muscle strengthening and range of motion exercses are started.

Despite adequate treatment recurrent hemarthroses are occasionally encountered. This condition justifies changing from a program of episodic treatment to a program of prophylactic therapy. If cessation of bleeding is not effected, immobilization with splints or a brace is indicated. A physiotherapy program, to prevent atrophy and stiffness, should be instituted. Synovectomy has been advocated for recurrent hemarthrosis (14), but its use is not recommended as it is usually possible to control bleeding on a prophylactic program and synovectomy usually results in restricted motion.

Patients with inhibitors to the missing clotting factor should be treated with immobilization, ice, muscle relaxants, and analgesics. New treatment regimens are being investigated.

Conservative Rehabilitation

The importance of physical therapy and the role of the therapist in the "hemophilia team" is treated in another article in this monograph. The aim of therapy should be to increase function by increasing muscle strength, maintaining or increasing range of motion and decreasing deformity. A record of joint motion, muscle testing, leg lengths, and circumference measurements should be kept and repeated at least yearly.

A severe flexion contracture or subluxation at the knee usually requires cast correction before therapy is started. If the contracture is less than 25° and subluxation not present, a well padded wedge cast can be employed. If wedging is done slowly factor replacement is not required. If the deformity is greater than 25° or subluxation is present, a Quengle cast (2) or desubluxation hinge is required. The correction should be applied slowly and if correction is not achieved after three weeks, a period of rest is recommended. Correction past 10° and complete correction of the subluxation are rarely achieved. After correction is achieved, a program of therapy to prevent recurrence is started. I employ a period of bracing, utilizing a polypropalene Hessing Orthosis with a Schleeker Lock (2). The brace is kept locked for a few weeks. After sufficient quadriceps strength is achieved the lock is opened during the day and reapplied at night. After two to three months the brace is discarded during the day and worn locked at night for a total of six months.

In the patient with a known inhibitor this brace is occasionally necessary to control recurrent hemorrhage.

Synovitis

Synovitis is a problem increasingly noted in the teenage hemophiliac. The clinical findings are a grossly distended but not tense or painful joint (usually the knee). It is associated with significant muscle atrophy, but a good range of motion is usually maintained (Fig. 17). The x-ray does not reveal advanced arthropathy and the changes are usually limited to epiphyseal osteoporosis, mild joint space narrowing, and subchondral irregularity. Clinically there is an incomplete response to a program of replacement therapy. If aspirated, blood-stained joint fluid is obtained. Hematocrit determinations have ranged from 8 to 30% and enzyme levels are elevated. If left untreated, capsular and ligamentous laxity may follow and rapid joint degeneration has been recorded. Occasionally the synovitis will regress for no apparent reason.

Recommended therapy has included prophylaxis, immobilization, physical therapy, repeated aspiration, oral and intraarticular steroids, and neglect. We have achieved most success with a program of prophylaxis, physical therapy and oral steroids (Prednisone 1 mg per Kg per day for one week followed by 0.5 mg per Kg per day for a second week). The initial response is striking but many cases relapse when the steroids are discontinued. If the synovitis persists for six months, synovectomy is recommended. Surgical synovectomy is performed, but despite early range-of-motion exercises some motion is always lost. Chemical synovectomy with osmic acid and radioactive gold are under investigation but long term followup is not available.

Soft-Tissue Hemorrhage

Clinical picture

Bleeding into the soft tissues of the extremities is quite common. Superficial hematomas are frequently seen, but usually resorb without sequelae. Bleeding into the deep muscle masses is more significant and if untreated may result in adjacent joint contracture and pressure neuropathy. The extent of damage depends upon the extent of hemorrhage and the containment provided by the various fascial compartments. Small hematomas in large muscle masses resorb without complication. Similar hematomas in tight fascial compartments will cause significant ischemic myopathy and neuropathy. Large hematomas, even in large unrestricted muscle masses, will resorb slowly and be replaced by large fibrous tissue masses which limit the excursion of the muscle and secondarily of the adjacent joints.

Treatment

As with arthropathy, it is of prime importance to stop the bleeding by replacing the missing clotting factor. The limb must be splinted and motion and weight-bearing eliminated. Well-padded plaster splints are best for this purpose and should be changed frequently as the contracture decreases. Physiotherapy should be started only after all evidence of acute bleeding, such as pain, warmth and tenderness, have disappeared. Isometric exercises maintain strength, but stretching frequently causes recurrence and should be avoided for quite a while. Similarly, weight-bearing should be begun very cautiously.

Specific sites

1. *Gastrocnemius-soleus.* The gastrocnemius-soleus is the most common site of muscle hemorrhage in the hemophiliac. Swelling at the calf and an equinus position at the ankle are seen. Levels of 50% should be achieved for as long as there is evidence of acute hemorrhage. A long leg plaster splint

should be applied in a position of comfort and weight-bearing eliminated. The splint should be changed every three or four days and the knee and ankle extended as much as comfort allows. It may take over six weeks to achieve a neutral position. Weight bearing should be delayed until the equinus contracture is less than 15 to 20° as otherwise increased flexion and strain may be placed on the knee (15). Once a contracture becomes permanent it is difficult to correct by conservative methods. Wedge casting may cause damage to the talus and is usually unsuccessful. Passive stretching yields similar results. Tendo-achilles lengthening should be considered before adaptive changes occur at the ankle.

2. *Iliopsoas*. The iliopsoas is a large muscle group and extensive hemorrhage with minimal symptoms may occur. The earliest sign is a flexion deformity at the hip. This can be differentiated from a hemarthrosis in that rotation is possible and usually not painful. Bleeding may be extensive, expanding into the retroperitoneum, and a drop in hemoglobin of four grams is not unusual. The patient walks with a flexion deformity at the hip and a secondary lumbar lordosis. The iliacus muscle is palpable above the iliac crest. As the pressure increases, the femoral nerve may be pressed against the inguinal ligament and a neuropathy results. There may be numbness over the distal thigh and proximal leg, quadriceps weakness or paralysis and diminution of the knee reflex (16, 17).

Factor levels of 50% should be maintained until pain and tenderness in the area of the iliacus muscle subsides. This may require over ten days of treatment. The patient should be kept at strict bed rest with the leg elevated on pillows. Bucks traction is not applied during the first few weeks and should be used cautiously as recurrence is common. If the patient can handle crutches he can be allowed up where the contracture is less than 30°, but weight-bearing is not allowed until it is 20°. These are generalizations and each case must be individually evaluated (15).

If there is femoral neuropathy recovery will be slowed. It may take over six months until strength returns and in 10 to 20% of the cases the damage may be permanent. While the quadriceps is weak the knee must be protected with a brace or splint as buckling may occur followed by hemorrhage into this joint.

3. *Forearm*. Bleeding into the tight fascial compartments of the forearm is an emergency. Volkmann's ischemic contracture with resultant deformity at the hand is common if treatment is not begun immediately. Factor levels of up to 100% and splinting are required. Hematologic evaluation for surgery should be started and the neurocirculatory status monitored closely. If replacement therapy is started rapidly, surgical decompression is usually not necessary. Similar treatment and observation should be instituted for bleeding into the carpal tunnel.

Pseudotumor Formation

Pseudotumor formation is a bizarre manifestation of hemophilia that may be a threat to both life and limb. Its incidence appears to be on the decline and it is rare in a well-treated hemophilia population. There are two clinical patterns (18, 19). In the adult population, it is most common in the pelvis and femur, areas in which there is proximity of large muscle masses to bone. A slowly expanding mass is noted following a history of trauma. The pseudotu-

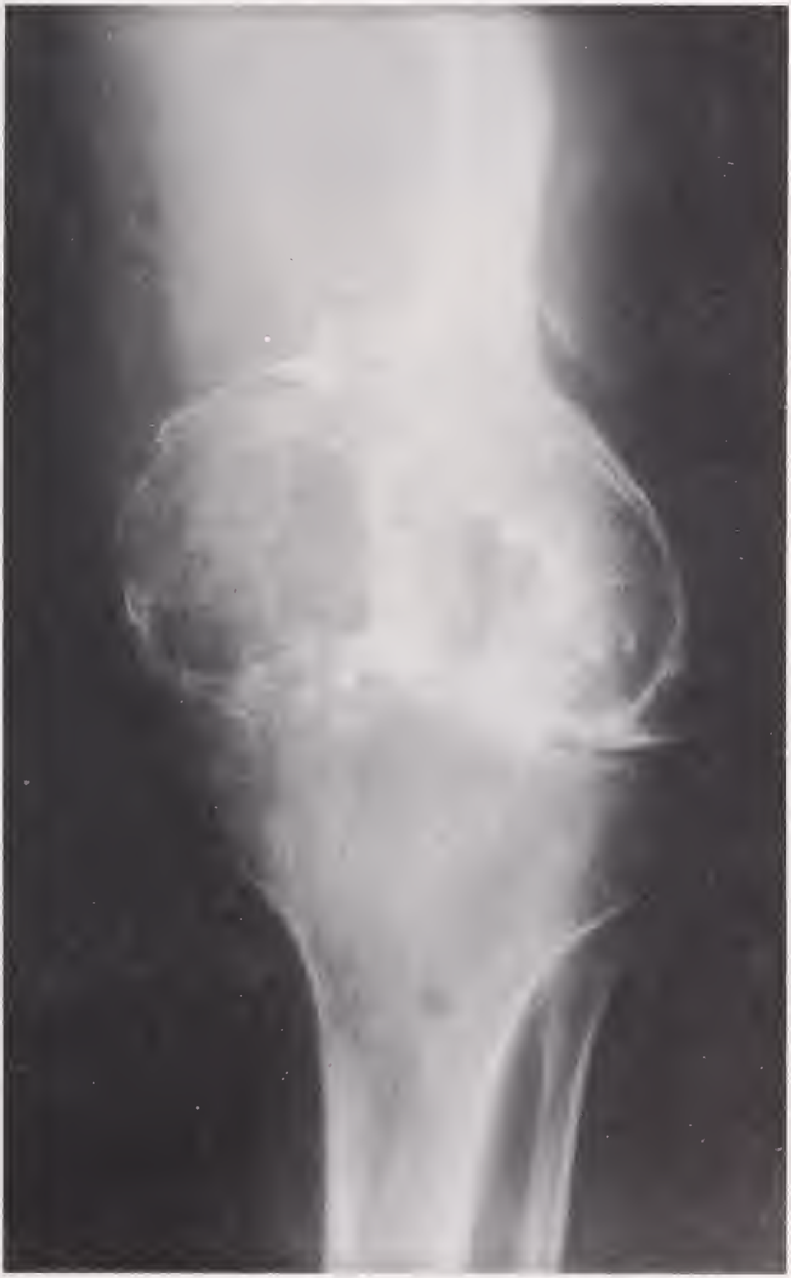

FIG. 11. Femoral pseudotumor.

mor may take 20 years to develop. In the younger hemophiliac the pseudotumor is frequently noted in the small bones of the hand and foot. Its appearance is rapid and multiple lesions are common.

By definition a pseudotumor must show evidence of a soft tissue mass associated with local bone destruction. At the femur there is evidence of periosteal stripping and extrinsic pressure necrosis of bone. There may be calcification or ossification within the soft tissue mass (Fig. 11). At the ilium the common picture is of pressure necrosis and a mass without periosteal reaction (Fig. 12). An IVP will show displacement of the ureters and bladder.

When pseudotumors occur before skeletal maturity, they are most common distal to the knee and elbow. The picture is one of cortical expansion and it has been suggested that the etiology is intra-osseous hemorrhage.

A multiloculated cystic mass is noted on gross examination. On microscopic examination there is a fibrous tissue wall surrounding coagulated blood. Calcification can be noted within the specimen. Areas of pressure necrosis of bone are seen (Fig. 13).

If left untreated the pseudotumor may result in fistulization through the skin, destruction of adjacent neurovascular bundles and pathologic fracture. Conservative treatment of distal pseudotumors is usually successful. Long-term replacement therapy is required. The level and duration of treatment must be judged from the clinical response. Immobilization in plaster should be utilized. Radiation therapy has been successful in several cases and can be considered if there is no response to repalcement therapy and immobilization (20, 21).

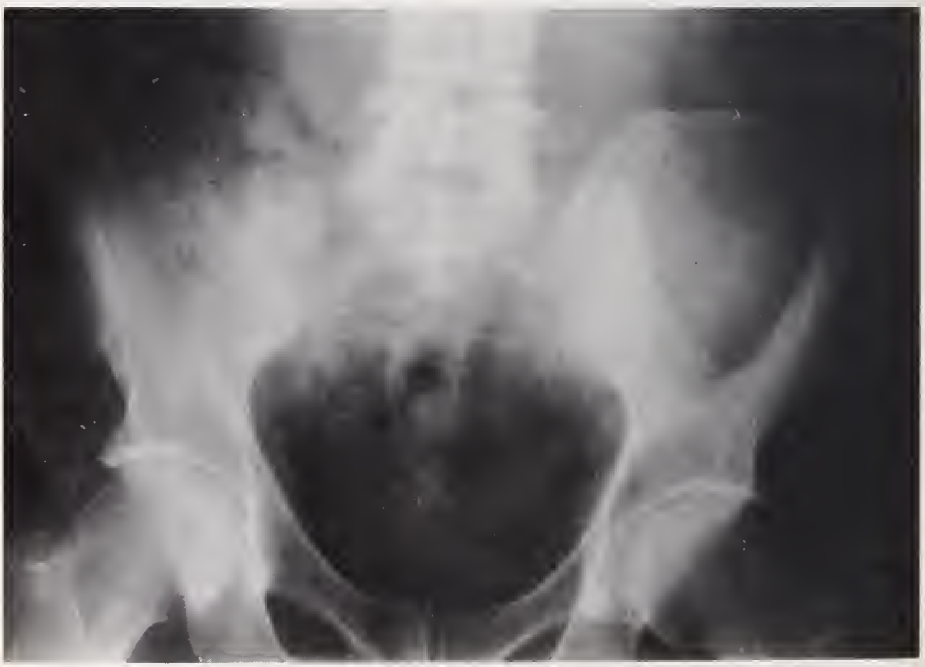

FIG. 12. Pelvic pseudotumor.

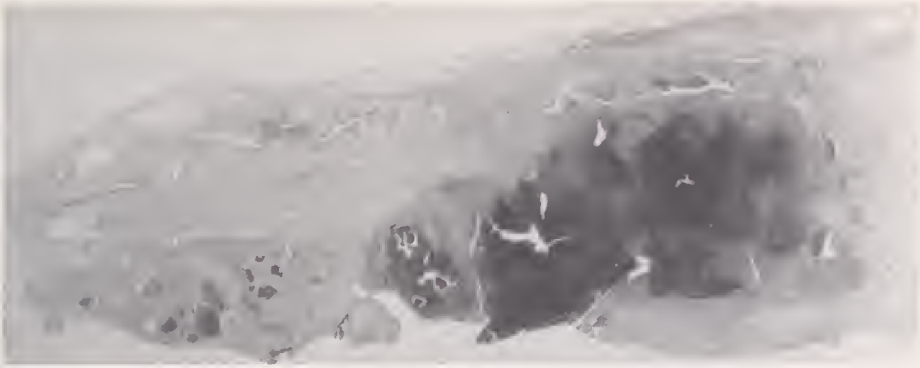

FIG. 13. Microscopic section from pseudotumor shown in figure 11.

An established pseudotumor in the proximal skeleton of the adult does not seem to respond to conservative therapy and surgical excision is recommended. This should be done before there is significant involvement of local structures.

Fracture Care

Fractures are not uncommon in the hemophiliac. Osteoporosis and limitation of joint motion predispose to fracture following relatively mild trauma. Fractures about the knee and hip are most common. If trauma is mild, x-rays may not be obtained and over 30% of these fractures are first treated as hemarthroses. A high index of suspicion is necessary.

If replacement therapy is started quickly, undue hemorrhage is not a problem. Levels of 50% maintained for one week are usually sufficient. Reduction of the fracture should be performed and the limb splinted or placed in traction. Circular casts can be used if bivalved and followed closely. It has been postulated that hemorrhage is limited because of the liberation of tissue thromboplastin. There is no evidence that union is delayed and routine fracture care can usually be followed. We recommend hospitalization for the first days even if all seems to be going well.

Conservative care is to be preferred, but if open reduction is necessary the patient should be evaluated as outlined previously. If there is no hematologic contraindication the surgery should be performed.

References

1. Konig, F.: Diseases of Joints in Bleeders, Reprinted in: Clin Orthop 52:5, 1967.
2. Jordan, H.: *Hemophilic Arthropathies*. Charles C Thomas, Springfield, Il. 1958.
3. Gilbert, M. and Cockin, J.: An Evaluation of the Radiologic Changes in Hemophilic Arthropathy of the Knee. In *Haemophilia*. Edited by F. Ala and K. W. E. Denson. Exerpta Medica, Amsterdam, 1973.
4. De Palma, A. and Cotler, J.: Hemophilic Arthropathy, Clin Orthop 8:163, 1956.
5. Hilgartner, M.: Hemophilic Arthropathy, Adv Ped 21:12p39, 1970.
6. Kingma, M.: Overgrowth in Hemophilia, Clin Orthop 39:199, 1965.
7. Swanton, M. Hemophilic Arthropathy in Dogs, Lab Invest 8:1269, 1959.

8. Astrup, T. and Sjolin, K. E.: Thromboplastin and Fibrinolytic Activity of Human Synovial Membrane and Fibrous Capsular Tissue, Proc Soc Exp Biol Med 97:852, 1958.
9. Hough, A., Banfield, W., and Sokoloff, L.: Cartilage in Hemophilic Arthropathy, Arch Path Lab Med 100:91, 1976.
10. Oronsky, A., Ignarro, L., and Perper, R.: Release of Cartilage Mucopolysaccharide-Degrading Neutral Protease from Human Leucocytes, J Exp Med 138:461, 1973.
11. Hilgartner, M.: Degenerative Joint Disease, Ann NY Acad Sci 240:340, 1975.
12. Duthie, R., Matthews, J., Rizza, C., and Steel, W.: *The Management of Musculo-Skeletal Problems in the Haemophiliac*. Blackwell Scientific Publications, Oxford, 1972.
13. Mackay, S. R., Gilbert, M. S., Kock, K., and Schumacher, P.: Early Management. In: *Comprehensive Management of Musculoskeletal Disorders in Hemophilia*. Edited by N. McCollough. National Academy of Sciences, Washington, D.C., 1973.
14. Storti, E., Traldi, A., Tosatti, E., and Davoli, P.G.: Synovectomy, A New Approach to Haemophilic Arthropathy, Acta Haemat 41:193, 1969.
15. Boone, D.: *Comprehensive Management of Hemophilia*. F. A. Davis Co. Philadelphia 1976.
16. Goodfellow, J., Fearn, C., and Matthews, J.: Iliacus Haemotoma. A Common Complication of Haemophilia, J Bone Joint Surg 49B:748, 1967.
17. Brower, T. and Wilde, A.: Femoral Neuropathy in Hemophilia, J Bone Joint Surg 48A:487, 1966.
18. Gilbert, M.: Characterizing the Hemophilic Pseudotumor, Ann NY Acad Sci 240:311, 1975.
19. Ahlberg, A.: On the Natural History of Hemophilic Pseudotumor, J Bone Joint Surg 57A:1133, 1975.
20. Chen, Y.: Bilateral Hemophilic Pseudotumors of the Calcaneus and Cuboid Treated by Irradiation, J Bone Joint Surg 47A:517, 1965.
21. Hilgartner, M. and Arnold, W. Hemophilic Pseudotumor Treated with Replacement Therapy and Radiation, J Bone Joint Surg 57A:1145, 1975.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May-June, 1977
Printed in U.S.A.

Rehabilitation Medicine and the Hemophilic Patient

JERRY WEISSMAN, M.D.

There are several manifestations of Hemophilia A or B which might benefit from the therapeutic techniques available from a rehabilitation medicine department. Most notable is the arthropathy so commonly seen in severe and moderate hemophiliacs that results from repeated joint hemorrhages. The joint most frequently involved is the knee, being affected in up to 80% of severe and 50% of moderate hemophiliacs (1). The elbows and ankles are the next most commonly involved, and 66% of severe hemophiliacs affected, and 50% of moderate hemophiliacs affected. The hips, shoulders, and wrists may also be affected. The small joints of the hand, feet and spine are spared. In addition, neurogenic complications following hemorrhages affecting the ulnar, medial, peroneal, sciatic, femoral and facial nerves have been reported (2, 3). Ahlberg (1) had one case of paraplegia following hematomyelia.

Bleeding into muscles with resultant contracture and subsequent joint dysfunction is not infrequent, reported in nine out of 95 cases of severe disease studied by Ahlberg. The most common muscle involved in this way is the gastrocnemius resulting in an equinus deformity of the ankle. Flexion contracture of the hip resulting from bleeding into the psoas muscle and flexion contracture of the fingers secondary to hemorrhage into the forearm are also seen. Hemophilic pseudotumor can produce disability via compression of nerves or destruction of weight-bearing bone, the latter on occasion resulting in amputation. Finally, hemophiliacs may also be subject to any of the other neuromuscular conditions seen in the general population.

The disability resulting from these neuromusculoskeletal complications of hemophilia has been estimated by Ahlberg (1). On a disability score of 0–3 with 0 being no disability and disability defined on the basis of a) the degree of arthropathy, b) the use of orthopedic devices and c) ambulation and activity of daily living skills, he found the following:

Severity of Hemophilia			Degree of Disability			
			0	1	2	3
Severe	10	2 patients	20	24	40	18
Moderate	6	5 patients	32	15	8	4
Mild	8	1 patients	78	2	1	

A breakdown by age showed a steady increase in disability to age 15 with little change in classification after the age.

From the Department of Rehabilitation Medicine, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

The underlying hemorrhagic disorder plus the above described physical impairments results in significant socioeconomic, vocational and educational disability (4, 5). The purpose of the hemophilia clinic at The Mount Sinai Hospital is to reduce this disability. The purpose of this paper is to describe the role of physical methods of treatment in this process. As with all other methods of management, changes in our approach have reflected the evolutionary changes in the nature and availability of replacement therapy.

The methods used in treating the neuromuscular problems referred to above in the nonhemophiliac might include various forms of superficial and deep heat, cold, iontophoresis, manipulation, massage, stretching and exercises. We will now describe how the application of these modalities have been and are used when there is, in addition, the underlying hemophilic disorder.

Review of the literature

In 1961 Austin et al (6) wrote on the use of physical therapy modalities in treating the residuals of hemophilia. Ultrasound at .3-.4 watts/cm2 × 2–3 minutes was reported to have sped up the resolution of superficial hematomas. This dosage would seem to be at the lower end of the therapeutic range (7). They also used interrupted galvanic stimulation without defining the parameters but stated it did not prove effective insofar as speeding the resolution of hematomas.

When treating established joint contracture without acute symptoms, a program of hot packs followed by gentle passive and active stretching was attempted. They reported no known instance of bleeding resulting from this gentle stretching. Electrical stimulation of muscles was used in the early phases of the muscle retraining program even when around joints recently involved with hemorrhage. Static exercises and resistive exercises under water were used as a prelude to active exercises against gravity. Resistive exercises were then given, at first manually and subsequently with weights. Swimming was encouraged as the "only safe, active sport" for patients with hemophilia.

Boone in 1966 (8) again refers to the use of ultrasound at a dose of .3-.6 watts/cm2 for 3–5 minutes and the use of electrical stimulation of muscles as part of a muscle retraining program. Also described in the technique of hyaluronidase iontophoresis.

Iontophoresis refers to the transfer of ions throughout the skin by means of an electrical current. Hyaluronidase is an enzyme which hydrolizes hyaluronic acid, a constituent of interstitial tissues, which serves as a physical barrier to the movement of liquids and solids. When the viscosity of the interstitial tissues are reduced, fluid diffuses more easily and a larger surface area is thereby available for resorption into the lymphatic and capillary network. Adding hyaluronidase to subcutaneously injected fluid markedly increases its rate of removal. The use of hyaluronidase ionotophoresis in other conditions, such as scleroderma and lymphedema was reviewed by Harris (9).

Boone thus applied the technique in an attempt to speed the resolution of soft tissue and joint hemorrhages. Subjective observations suggested a more rapid resolution. A controlled study in 1969 (10) failed to demonstrate any significant differences in hemophiliacs recovering from soft tissue or joint hemorrhages when treated with hyaluronidase iontophoresis.

Boone (8) also described an exercise program, begun when a hemorrhage is almost resolved with pain and swelling diminished and motion increasing. The program is initiated with the use of isometric exercises. Rhythmic stabilization and hold relaxation techniques are also used. These are so-called proprioceptive neuromuscular facilitation exercises (11), having an active-assisted/active-resisted quality and reputed to produce good muscle contraction with little joint stress.

Heavy resistive exercises were used in patients with mainly chronic joint problems with a program for the entire body included. Caution was advised in exercising the lower extremities after a retroperitoneal bleed, especially those exercises involving hip extension. Pool therapy with the water providing both support and resistance, with the use of waterproof splints when necessary, is also advocated.

In 1974 Boone (12) reviewing the methods used at the Orthopedic Hospital of Los Angeles, noted that exercise programs were the same as those used for nonhemophilic patients with similar musculoskeletal problems. Daily coverage with replacement therapy was used when weakness and deformity were severe and an intensive exercise program was to be instituted. Swimming, bicycling, tennis, gardening, and hiking were recommended for recreational activities.

Dietrich, writing in 1975 (13), discussed the importance of preventing deformity and and the maintaining of good musculoskeletal function of the younger hemophiliac. In addition, she discussed the nonsurgical management of established deformities and degenerative arthritic changes in the joints of the older patient. Children are encouraged to participate in age-appropriate activities. For school age boys, a modified physical education program is recommended, avoiding contact sports such as football, wrestling and basketball. Swimming, tennis, hiking and gardening are encouraged. Exercise programs similar to the ones already described are advocated for the arthritic deformities seen. Poor results with repeated shoulder and elbow hemorrhages are reported with mention of the use of irradiation for the chronically painful shoulder in the adult to produce palliation of symptoms.

The Rehabilitation Medicine Department and the Hemophilia Clinic at The Mount Sinai Hospital

Three members of the department attend the clinic regularly, a physician specialist in physical medicine and rehabilitation (physiatrist), a physical therapist and a vocational counselor. The services of an occupational therapist have been used up until now only for the fabrication of splints. In the future we hope to expand this role to include such activities as evaluation of fine and gross hand activities, prevocational evaluation, and occupational therapy to increase the strength and the range of motion of the upper extremity.

The role of the vocational counselor will be discussed in a separate article in this issue of the journal (5).

The three people involved with the management of the musculoskeletal problems of the hemophiliac are thus the orthopedist, physiatrist, and physical therapist. A neurologist is immediately available for consultation. The fundamental role is played and overall direction given by the orthopedist who is also codirector of the clinic. There is some inevitable overlapping of roles that, in the case of our clinic, has, if anything, been a positive factor.

Each patient receives a detailed range of motion and manual muscle examination (Fig. 1). The presence of subluxation, rotational deformities, leg length discrepancies and joint instability are noted. The circumference of the calf and thigh are recorded routinely as well as the circumference of upper extremity segments when they are significantly involved. A functional evaluation is made, using a questionnaire requiring information about such things as maximal distance a patient can walk, ability to climb stairs, use of orthopedic and assistive devices, problems with activities of daily living, schooling, vocational history and participation in recreational activities.

Patients are advised as to general types of activities to promote physical fitness. Swimming is encouraged for all. Then, depending on the status of their joints, jogging, bicycling, tennis, golf, dancing, croquet, ping pong, fishing or shuffle board might also be suggested. Football, wrestling, jumping rope, basketball, volley ball, roller skating, horseback riding, trampoline jumping are the types of activities we do not encourage. One will find some variation in the lists of acceptable sports activities allowed for the hemophil-

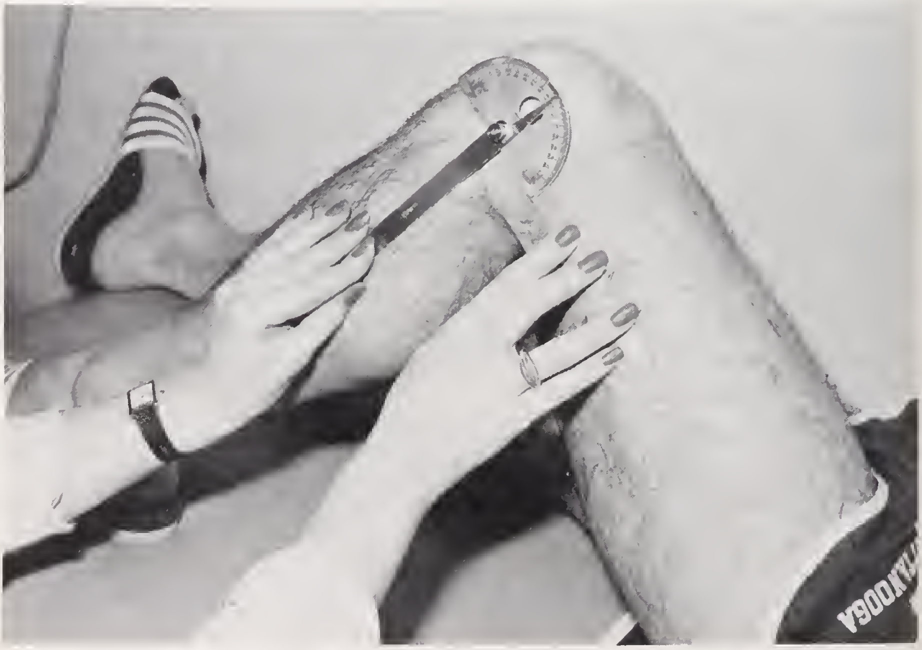

FIG. 1. Measuring range of motion of the knee with a goniometer.

iac. Lazerson, (14) commenting on the approach used at Children's Hospital in Los Angeles, notes that modified forms of baseball, non-tackling football and basketball are allowed and Seeler, (15) who is director of a camp for hemophiliacs, includes trampoline jumping as part of her total program. Factors such as the availability of adequate supervision and home therapy programs explain the difference.

There is a general feeling among people who work with hemophiliacs that those patients who maintain good general levels of physical fitness and are well muscled have fewer "spontaneous hemorrhages." I could not find any references of controlled studies which clearly substantiate this feeling. There is work that shows an increase in factor VIII levels in normal people after exercise (16, 17) but a similar response has not been found in the hemophiliac. Nevertheless, a joint surrounded by normal musculature should be less susceptible to the stresses of routine and athletic activities. The effects of a physical training program on muscle fiber size in patients with rheumatoid arthritis have been described and are probably applicable to the hemophiliac (18). In addition, the role of athletics in the social and psychological rehabilitation of the hemophiliac should not be underestimated. Patients with established arthropathies or those showing a tendency to having trouble with a particular joint are begun on specific exercise programs. Some of the modalities reviewed in the previous section are used but not emphasized, the exercise portion of the program being considered the more important aspect of the program.

A decision is made jointly by the orthopedist and hematologist as to the use of replacement therapy to cover the exercises. Factors considered are the severity of the problems, the intensity of the program, the methods used and the goals.

Hyaluronidase iontophoresis has not been used in our clinic. Modalities such as short-wave diathermy and ultrasound have been used with some success in treating various arthropathies (7). Most evidence, with some dissenters (19), supports the contention that their effects are all due to the increase in temperature of the tissues treated, their uniqueness being in their ability to heat deeper structures such as muscles and joints. Their benefits are to be a reduction in "muscle spasm" and pain plus an effect on the extensibility of scarred synovium and thickened joint capsules of fibrotic muscles. In spite of their potential benefits, we do not use these methods. Superficial heating modalities such as hot packs and whirlpool can produce the desired muscle relaxation and decrease in pain and do not have any of the potential disadvantages of the deep-heating modalities.

These disadvantages include the damage of small blood vessels. This effect alone has caused bleeding diatheses to have been considered a contraindication to the use of deep heating. If necessary, however, this could be overcome with the prior use of replacement therapy. Replacement therapy would, however, have no effect on other disadvantages of deep heating—effects such as acceleration of bone growth of young people, a problem some patients with hemophilia already have. In addition, the intraarticular temperature may be increased. This may be of some special importance in hemophilia where the mechanism of joint destruction, at least during certain stages, has been likened to that in rheumatoid arthritis. In rheumatoid arthritis the process of joint destruction is mediated by an enlarged irritated synovium secreting collagenases and lysosomal hydrolases which then destroy other joint structures. Collagen was found by Harris et al (20) to be somewhat resistant to these enzymes at 33° but at 36° collagenolysis was increased by a factor of 4. Hollander (21), extrapolating from this fact, suggested that deep heating would be deleterious to joints suffering from an inflammatory arthropathy since the heating can raise intraarticular temperatures to 40°C which then may persist for several hours. Superficial heating, on the other hand, temporarily decreases joint temperature by shunting blood flow to more superficial tissues and ice packs after a brief initial increase in temperature then decrease joint temperature 2–3°C for several hours.

The importance of these findings in hemophilia derive from the finding that hemophilic arthropathy may also be mediated via the release of hydrolytic enzyme (22) from an enlarged inflamed synovium.

Cold, referred to briefly above, is mentioned frequently in the hemophilia literature (23). Traditionally used as adjunct therapy in an acute joint hemorrhage it can also be of help in treating established arthropathy, usually when there is an associated synovitis. Cold has many effects but only a few are thought to be therapeutic (7). Short applications usually have a cooling effect only on skin, with fat acting as a barrier to the cooling of underlying muscle; however, with longer application the effect on skin is modified by the adjustments of local circulation while the effect on muscle may continue for several hours. The induced vasoconstriction can reduce posttraumatic hemorrhages and lessen edema. The inflammatory response can be ameliorated, muscle tone and pain decreased.

Cold therapy can be used in the form of cold packs, iced water immersion, ice massage or refrigerant sprays. Cold is contraindicated in those who demonstrate Raynaud's phenomenon, so-called cold allergy manifested by the development of hives, and joint pain in the condition known as paroxysmal cold hemoglobinuria (24).

The techniques of massage and manipulation were not referred to in the literature dealing with the management of hemophilia and are not used routinely in our clinic. As pointed out by Kamenetz (25), the inability to prescribe these therapies in exact constituents, the paucity of research plus the impossibility of avoiding subjective factors have led to the rejection of these techniques by many physicians. Nevertheless, the techniques of peripheral joint manipulation as described by such authors as Menell (26), Cyriax (27), and Maitland (28) have had reports of good results extending over many years.

Almost universally they have been considered contraindicated in joints that are inflamed. Whether some of these techniques would have some value in the quieter phases of hemophilic arthropathy remains a subject for study.

Stretching, a technique somewhere between passive range of motion and manipulation (25), when used properly, can prevent contractures, eliminate early muscle tightness and prevent early formation of adhesions. For example, the constant pull of tight hamstring against the tibia and fibula may cause posterior subluxation of the tibia on the femur, the tight hamstring having developed secondary to keeping a painful knee in the flexed position. Active stretching of the joints, that is to say stretching done by the action of one's own muscles as they pull on the structures surrounding adjacent joints, is made part of the general conditioning program. Purely passive manual stretching is done only under unusual circumstances. Stretching of established joint contractures is most effective when done slowly over relatively long periods. An example of this is the use of the Quengel cast or cast wedging (29) which in our clinic is done under the direct supervision of the orthopedist.

The above modalities are used as noted but in treating the arthropathy of specific joints the emphasis is placed on the exercise program. The sequence of events, as we see it, leads from joint hemorrhage with pain and inflammation to limitation of motion and subsequent deformity resulting in a deconditioning and atrophying of muscles and ultimately weakness with loss of motor skills and coordination. The goal of the exercise program is of course to prevent, retard or reverse this progression.

The exercise program is individualized for each patient. The limb and joint to be treated are specified as well as the objectives, duration of treatment, frequency, precautions and date of reevaluation. The program is revised based on the response to the initial prescription.

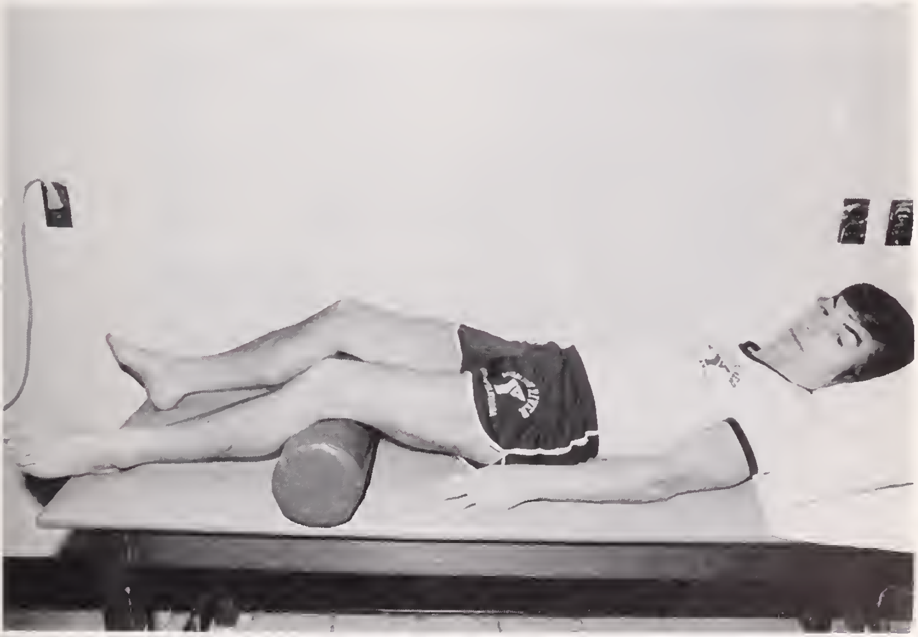

FIG. 2. Isometric exercises for the quadriceps with the knee in slight flexion—the subject is a physical therapist and does not have hemophilia.

The exercise program may be taught to the patient as part of his visit to the hemophilia clinic. If there is any question that the instruction might not be understood, the patient will be scheduled for several sessions in the Department of Rehabilitation Medicine until we are sure the program is performed correctly. Alternatively, when it is felt desirable, the whole program will be carried out on a daily or three times a week basis in the Department. Factors which may contribute to this decision include the need for modalities or other equipment not available at home or more importantly, the exercises require the assistance of a trained physical therapist.

There is no absolute contraindication to any of the standard exercise techniques including isometric, isotonic, isokinetic or PNF (Fig. 2–3). The determining factor is usually the condition of the joint at the time the exercises are started. If weights are used for resistance, they should be placed whenever possible such that their effect is felt upon only one joint, e.g., placing cuff weight above the ankle when strengthening the knee rather than

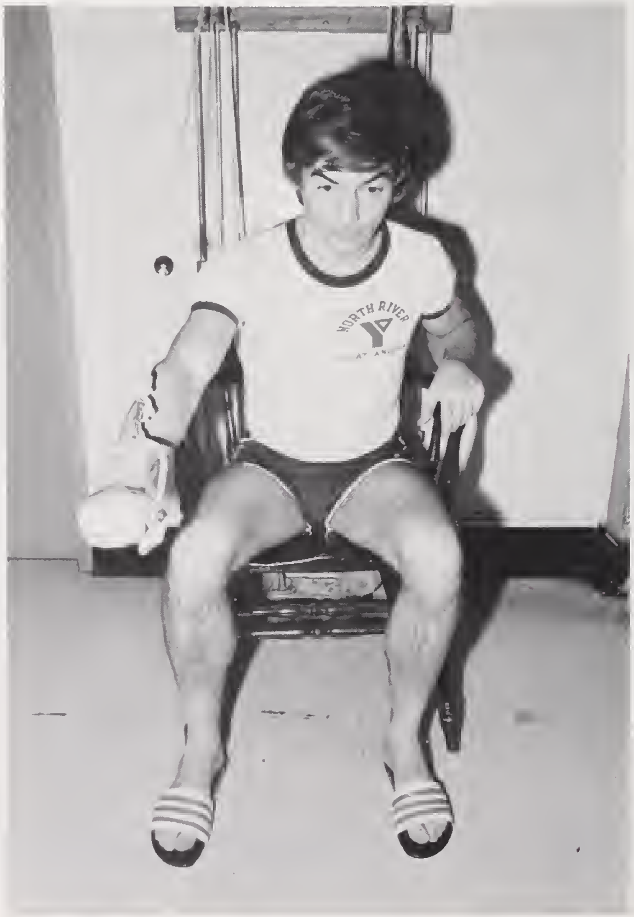

FIG. 3. Strengthening exercises for the upper extremities using wall pulleys.

on the foot which then also stresses the ankle. The key to all exercises is slow, gradual progression. When weights are used they are progressed by one pound increments. Minimal soreness felt the following day is not significant and the patient should be allowed to continue with the program. It is preferable to do the exercises at night or to allow one- to two-hour rest periods to obviate the patient using fatigued muscles for obligatory functional activities after exercises.

If a patient is first seen after an acute joint hemorrhage or if a hemorrhage occurs while the patient is on an exercise program, the following progression would be typical. Replacement therapy is given in adequate doses. The acute joint is splinted in the position of comfort. As the pain and swelling begin to diminish isometric exercises are begun. As the fluid continues to resorb active range of motion is encouraged. As the range of motion approaches normal, further strengthening of the surrounding muscles is carried out. When the

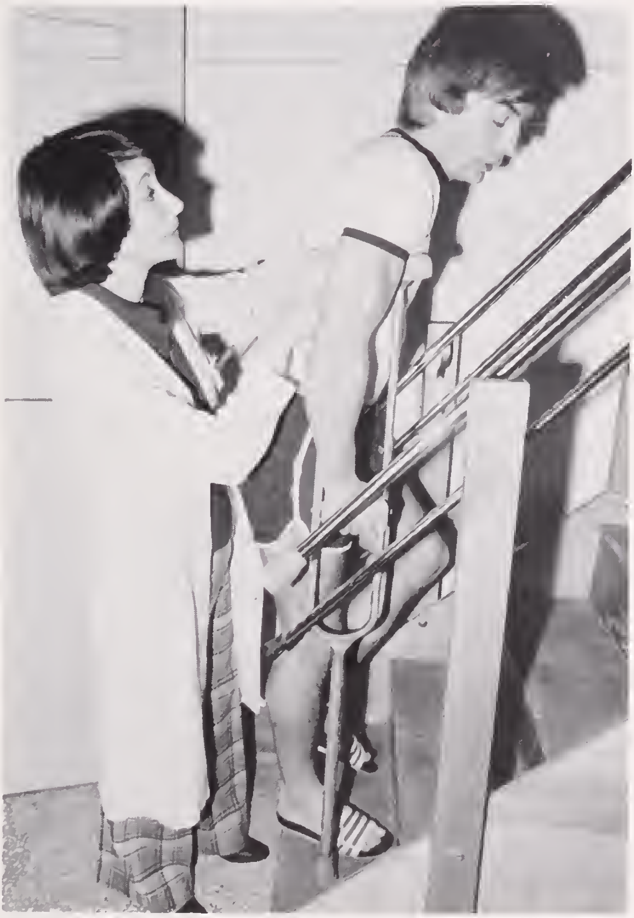

FIG. 4. Hemophilia clinic Physical Therapist Carolyn Zottoli demonstrates techniques of stair climbing, nonweight-bearing on the left leg postoperative to knee surgery.

muscles can support the limb against gravity plus resistance, normal activities are allowed.

Exercise programs are also used to prevent muscle atrophy and weakness when it has been elected to use long-term bracing of a limb or to restore muscle power prior to discontinuation of a brace, and finally as part of the postoperative management for patients undergoing orthopedic surgery (Fig. 4).

The use of assistive devices such as canes, crutches and walkerettes is the same as in the nonhemophiliac though one must anticipate the additional strain placed on the upper extremities and the intact lower extremity, (Fig. 5).

Of the 235 patients registered with the clinic, 128 patients were seen by the team this past year, 1975. 64 patients were instructed in general conditioning programs. 39 were started on home programs related to a specific disability. An additional 25 patients were treated in the department; 18 of these as out

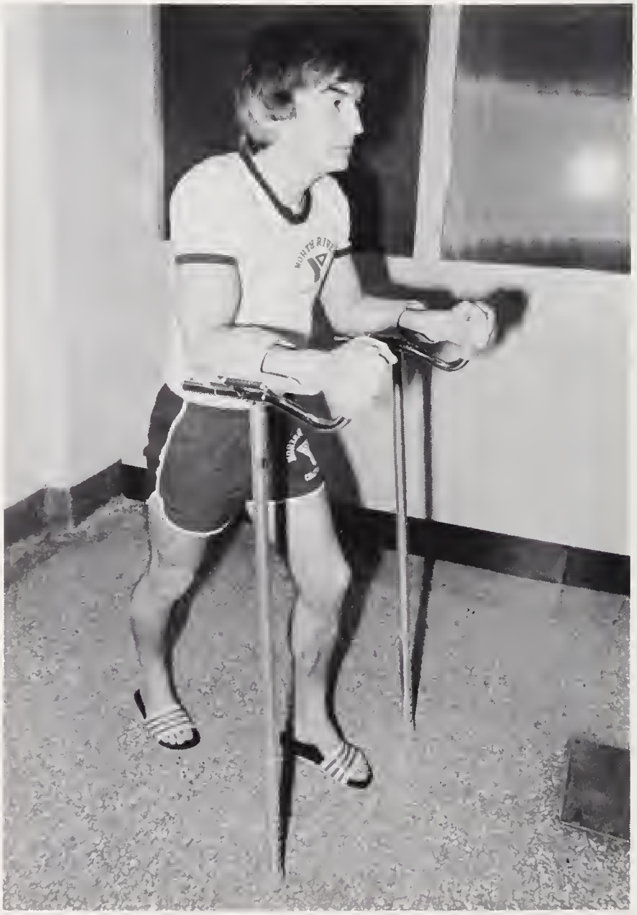

Fig. 5. Forearm crutches relieve some of the pressure on the elbow and wrist joints and require less triceps effort.

patients and 7 as inpatients. Of the 7 inpatients, 5 were postsurgery and 2 were admitted primarily for an intensive rehabilitation program. The average number of treatments for those seen in the Department of Rehabilitation Medicine was 8, with the range being 1–35.

Referring again to Ahlberg's series (1), he reported one patient who was bedridden and 8 who were confined to wheelchairs. Just recently we treated the first patient seen in our clinic who deteriorated to the point of being bedridden. This was a 69-year-old factor IX hemophiliac with level of less than 1% who six months previously had suffered a myocardial infarction and had not ambulated since. The patient had severe arthropathy of both knees, ankles, elbow and shoulders and even prior to the MI had ceased ambulation. He was admitted to the hospital and over the period of one month, using the approach described in this article, the patient reached the point of ambulating independently with a walkerette and is using this skill presently at a functional level. Two patients have been seen who presented to the clinic confined to a wheelchair; one at age 16, one at age 11. Both are now fully ambulatory.

Conclusion

1. The musculoskeletal problems of hemophiliacs contribute significantly to their total disability.
2. The potential for reducing their disability has increased in recent years with the advances in replacement therapy and the introduction of the comprehensive team approach.
3. Physical methods as described in this article can play an important role in this total process.
4. Continued observation will be necessary to confirm the expectation that the musculoskeletal problems of hemophiliacs will be greatly diminished for the patients who will be managed as above from their infancy.

References

1. Ahlberg, A.: Hemophilia in Sweden VII. Incidence Treatment and other Musculo-Skeletal Manifestations of Hemophilia A and B, Acta Orthopaedica Scandanavica Supplementum No. 77, 1965.
2. Aggeler, C. G. and Lucia, S. O.: The Neurological Complications of Hemophilia, J Nerv Ment Dis 99:475, 1944.
3. Silverstein, A.: Neurology in Hemophilia, JAMA 190:554, 1964.
4. Article by Wincott.
5. Article by Marshall.
6. Austin, E., Rolland, W., and Clausen, D.: Use of Physical Modalities in the Treatment of Orthopedic and Neurologic Residuals in Hemophilia, Arch Phys Med Rehab 42:393–397, 1961.
7. Lehmann, J. F. and De Lateur, B.: Heat and Cold in the Treatment of Arthritis. In *Arthritis and Physical Medicine*. Edited by Licht, S. 1969.
8. Boone, D. C.: Physical Therapy Aspects Related to Orthopedic and Neurologic Residuals of Bleeding, Physical Therapy 42: 1272–1281, 1966.
9. Harris, R.: Iontophoresis. In *Therapeutic Electricity and Ultraviolet Radiation* (2nd Ed.) New Haven, Ct., 1967.
10. Boone, D. C.: Hyalvronidase Iontophoresis, Phys Ther 49:139–145, 1969.

11. Knott, M., Voss, D. O.: *Proprioceptive Neuromuscular Facilitation* (2nd Ed.) Hoeber, New York, 1968.
12. Boone, D. C.: Management of Musculoskeletal Problems of Hemophilia, Phys Ther 54:122–127, 1974.
13. Dietrich, S. L.: Rehabilitation and Nonsurgical Management of Musculoskeletal Problems in the Hemophilic Patient, Ann NY Acad Sci 240:328–337, 1975.
14. Lazerson, J.: It's a New Ballgame for Hemophiliac Youngsters, Physician and Sportsmedicine. 3:63, 1975.
15. Seeler, R., Ashenhurst, J., and Miller, J.: A Summer Camp for Hemophiliacs, J Pediat 87:758–759, 1975.
16. Rizza, C. R. and Eipe, J.: Exercise, Factor VIII and the Spleen, Br Haematol 20:629–635, 1971.
17. Strand, C. L., Beene, J. R. et al.: Production of High-Potency Cryoprecipitate from Exercised Blood Donors and the Treatment of Hemophilia A with This Material, Am J Clin Path 62:496–501, 1974.
18. Nordemar, R., Edstrom L., Ekblam, B.: Changes in Muscle Fibre Size and Physical Performance in Patients with Rheumatoid Arthritis after Short-Term Physical Training, Scand J Rheumatology 5:70–76, 1976.
19. Cameron, B. M.: Experimental Acceleration of Wound Healing, Am Orthop Nov. 1961:336–343.
20. Harris, D. H., McCroskey, O. A.: Degradation of Cartilage Collagen by Rheumatoid Synovial Collagenase, New Engl J Med 290:1–5, 1974.
21. Hollander, J. L.: Collagenase, Cartilage and Cortisol, New Engl J Med 290:50–51, 1974.
22. Hilgartner, M. W.: Replacement Therapy and Prophylactic Treatment. In *Comprehensive Management of Musculoskeletal Disorders in Hemophilia*. Edited by N. M. McCollough. National Academy of Sciences, Washington, D.C. 1973.
23. DePalma, A. R.: Hemophilic Arthropathy, Clinical Orthopaedics and Related Research 52:145–165, 1967.
24. Choplin, H.: Hemoglobinuria. In *Textbook of Medicine*. Edited by Beesan, R., McDermott, W., W. B. Saunders, Philadelphia, 1971.
25. Kamenetz, H. L.: Massage, Manipulation and Traction. Licht, S., Elizabeth Licht, 1969.
26. Menell, J. M.: *Joint Pain*. Little Brown & Co., Boston, 1964.
27. Cyriax, J.: *Textbook of Orthopedic Medicine* (Vol. I). Williams & Wilkins Co., Baltimore, 1969.
28. Maitland, O. D.: *Peripheral Manipulation*. Butterworth, London, 1970.
29. Article by Gilbert.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May-June, 1977
Printed in U.S.A.

Hematologic Management and Surgery in Hemophilia

LOUIS M. ALEDORT, M.D.

Elective and emergency surgery in the hemophiliac is a challenge to the physician. At the present time we strongly feel that the following requirements should be met before surgery is undertaken.

1) A hematologist and diagnostic coagulation laboratory is available
2) The surgeon be familiar with the handling of a patient with a coagulation disorder
3) There be a blood bank capable of providing the appropriate replacement material
4) There be an appropriate rehabilitation team for postoperative management

At the present time, approximately 15–20% of hemophilia patients develop an inhibitor, an antibody which is capable of destroying the administered factor. It is therefore essential that screening for this inhibitor be mandatory prior to the institution of surgical intervention. If an inhibitor is present, surgery whould not take place. In the elective situation we recommend that the patient undergo an infusion study. This entails the administration of the missing materials in order to:

1) Determine the efficacy of the material in vivo.
2) Establish whether one can obtain the desired level.
3) Evaluate the half life of the material in order to program:
    a) requirements for the treatment,
    b) the total amount of material need for the 14 postoperative days

An initial dose is calculated to raise the patient's level to 60 or 70%. To calculate a dose one uses the following information.

100% of a given factor is equal to one international unit per cc of plasma. Plasma volume in an adult is 40cc per kilogram of bodyweight. An average person weighs 70 kilos and thus has a plasma volume of 2800 cc. If he were a 0% hemophiliac and one wished to elevate his level to 100% he would need 2800 international units. If fresh frozen plasma was being used one assumes that each cc of plasma has 1 unit and thus requires 2800 cc (an unworkable volume). If cryoprecipitate is used one assumes approximately 75–100 International Units per bag of cryoprecipitate, and thus approximately 28 bags would be required. If concentrates are used the specific amount of International Units contained in a vial is clearly stated and one can assume this to be correct in most instances. Samples are taken for factor assays before, 15

From the Department of Medicine, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

minutes after infusion and at appropriate intervals to determine the half life. The normal half life for factor VIII is about 12 hours and for IX, approximately 24 hours. (Figure 1) with both substances there is initial rapid followed by a slower disappearance. For Factor IX, twice as much material is required to achieve desired level, as approximately one half diffuses out of the introvascular space. On the morning of surgery the patient receives enough material to raise the level to 70% and is studied postoperatively to determine the success of the infusion and the amount lost via expected surgical bleeding. The patient is then reinfused at appropriate intervals to maintain a minimum level of 25–35% at all times. The knowledge of the half-life of the injected material is critical for the decision as to quantity required for the next dose to attain adequate hemostatic levels. One aims for infusions at 12-hour intervals. On the first and second postoperative days factor levels are usually required to determine appropriate therapy for the remaining 10–14 days.

Hazards to therapy

1) One must recognize that the fractionated materials used for replacement of hemophilia (VIII and IX) requires the utilization of multiple donors. Therefore, the material almost assuredly carries the hepatitis virus despite present negative australian antigen testing.

2) A low level of anti-A and anti-B antibodies cannot be totally removed from this material and when large quantities of factor VIII and IX are administered one may see hemolysis. Patients should be studied prospectively looking for early evidence of hemolysis. The Coombs test may become postive, the haptoglobin may fall and spherocytes are seen in the peripheral blood. Once recognized, and symptomatic anemia presents, it is important to replace blood with type 0 blood rather than the patients' specific type. Patients with type 0 blood do not run into this difficulty.

3) Thrombosis following the use of factor IX materials has been described and one must be aware that this is a possibility. The material, however, should not be withheld if emergency or elective surgery is necessary.

4) One must be aware of the fact that inhibitors can develop anywhere along the line, and if bleeding occurs which cannot easily be explained as a

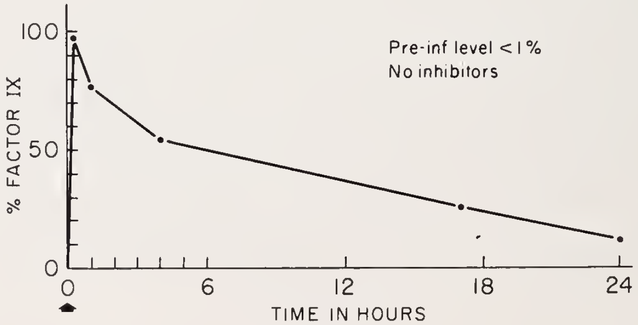

FIG. 1.

surgical problem, reexamination for the presence of inhibitor must be done. The management of inhibitor is a major problem and goes beyond the scope of this chapter.

Hemophiliacs have pain when they bleed spontaneously or following surgery. Analgesics containing aspirin, and classical anti-inflammatory agents (such as Butazolidine and Indocin) are in general contraindicated as they may potentiate the bleeding disorder by altering platelet function. It is important to assess analgesics for the presence of aspirin* (i.e. Percodan). Without replacement with hemostatic levels of factor, intramuscular injections should not be used.

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* Berger, S. and Aledort, L.: The Use of Analgesics and Anti-Inflammatory Agents in Hemophilia. In *Handbook of Hemophilia*. Excerpta Medica (In press).

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May-June, 1977
Printed in U.S.A.

Reconstructive Surgery in the Hemophiliac

MARVIN S. GILBERT, M.D.

The introduction of cryoprecipitate by Judith Pool in the early 1960's and the subsequent availability of concentrates have changed the orthopedic approach to the musculoskeletal complications of hemophilia. The added dimension of reconstructive orthopedic surgery can now be utilized. Prior to this, surgery was risky and the results unpredictable. Today, with adequate hematologic control, most any procedure can be undertaken (1). The literature has been saturated with reports of successful thoracic, brain and even open heart surgery.

However, as will be stressed in the report, a successful outcome is dependent upon the close cooperation of a team familiar with the care of the hemophiliac and upon close attention to details.

Hemophilia Team

The organization of the International Hemophilia Treatment Clinic (IHTC) at The Mount Sinai Hospital has been outlined in the introduction to this monograph. This team is set up to deliver comprehensive care and all elective procedures are discussed at our weekly patient care conferences.

While not all these members are required for successful hemophilia surgery, there are certain minimal requirements which are outlined below:

1) A hematologist conversant with the problems of hemophilia care.
2) A diagnostic laboratory capable of performing factor and inhibitor assays.
3) A complete blood banking facility.
4) An orthopedic surgeon familiar with the orthopedic complications of hemophilia.
5) A physiatrist and/or physiotherapist who can work with the orthopedic surgeon.

At our clinic we require that all patients for elective procedures be screened by our psychiatrist to make sure that they can handle the psychologic trauma of surgery. This is especially important in the older patient who lived in the era prior to adequate replacement therapy when death and loss of limb from surgery were a significant threat. Our patients are also screened by a financial counselor. The fee for factor replacement may run as high as $5,000-17,000 and it would be unfair to leave the patient with "crippling bills" after surgery. No patient has been refused surgery because of financial reasons, but it is better to determine the source of payment prior to, rather than after, surgery.

From the Department of Orthopaedics, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Marvin S. Gilbert, M.D., 1100 Park Avenue, New York, N. Y. 10028.

Hematology Evaluation

When the previously described arrangements have been completed, the patient is scheduled for surgery. A single batch of approximately 60–100,000 units of factor is then ordered for the patient and set aside in the blood bank. Once the surgery is undertaken this batch is reserved for the exclusive use of the patient, to insure adequate supplies during the postoperative period. The patient is admitted four days prior to surgery. As described by Aledort, a factor assay, inhibitor study and infusion study are undertaken. On several occasions the calculated dosage to achieve a hemostatic level was insufficient and the amount given had to be increased. If the half-life proves to be short, a new batch of factor should be tested and used. At the same time, the routine preoperative studies, including liver function tests, should be evaluated. Many of those patients have chronic elevation of their liver enzymes. If they are not markedly elevated and if there are no significant changes from previous studies, the surgical procedure can be undertaken.

If at all possible, surgery is scheduled for early in the day and early in the week. This ensures that most of the clinical and laboratory staff will be within the confines of the hospital for much of the postoperative period. The anesthesiologist must be warned not to order intramuscular premedications as hemostatic levels are not achieved until after the patient arrives in the operating room and an adequate intravenous is started. A large intracath is used and occasionally a cut down must be performed because of the poor state of the patient's veins. A second vein must be accessible to the anesthesiologist for collecting the factor assays required during the procedure. The required levels, the duration of treatment and frequency of assay are discussed in detail by Dr. Aledort. In summary, levels of 70–100% are achieved preoperatively and they are not allowed to go below 30%. For Factor VIII this usually requires infusion twice daily (once for Factor IX) until sutures are removed. If intensive physiotherapy is required, lower levels are maintained for another week or two.

Orthopedic Considerations

The recent surgical advances in the care of rheumatoid and osteoarthritis have been applied to the hemophiliac. The application of good orthopedic principles includes consideration of the fact that we are dealing with multiple joint involvement in a young, relatively active individual. Procedures employed should not put undue stress on adjacent joints and should have a good prospect of lasting the patient's lifetime. Upper extremity involvement (most commonly at the elbow) should be taken into account if a long period of time on crutches is required.

The common sites of musculoskeletal bleeding and the sequellae that may require surgery are listed in Table I.

Because of the expense and possible complications of replacement therapy, combined procedures are planned when possible. We have done herniorrhaphies, vasectomies and other clean procedures at the same time as orthopedic procedures. We have avoided procedures that might cause a transient bacte-

TABLE I

Sites of Musculoskeletal Hemorrhage

1. Joint
    - A. Arthropathy
    - B. Synovitis
2. Soft Tissue
    - A. Contracture
    - B. Neuropathy
3. Bone
    - A. Pseudotumor Formation

TABLE II

Surgical Procedures

ARTHROPATHY	
Radial head resection and partial synovectomy at elbow	7
Knee arthrotomy	4
Osteotomies about knee	6
Total hip replacement	5
Total knee replacement	1
SYNOVITIS	
Synovectomy	3
Patellectomy	1
CONTRACTURE	
Triple arthrodesis	4
Tendoachilles lengthening	1
Flexor tendon lengthening	1
PSEUDOTUMORS	
Amputation	1
Resection	3
FRACTURES	
Hip pinning	1
MISCELLANEOUS	
Toes	3
Debridement	1

TABLE III

Complications

Hemorrhage and infection	2
Infection	1
Minor postoperative bleeding	2
Inhibitor formation	?1
Hepatitis	1
Thromboembolism	0

remia (e.g., certain urologic or dental procedures). Oral surgery is frequently necessary and on occasion we will perform the surgery one week after the initial orthopedic procedure when the patient is still on high levels of replacement therapy. We have avoided such procedures when there are metallic implants present.

Certain technical aspects should be followed. All needles and sharps should be carefully discarded as the risk of hepatitis and contamination is high. Double gloves are recommended during the procedure and all sharp edged instruments such as rake retractors should be carefully replaced on the instrument table after use lest one of the surgical team is accidentally cut.

The surgical technique varies little from that used in the non-hemophiliac. Naturally careful attention is paid to surgical hemostasis. Electrocoagulation has been used in most of the cases without a problem. Tourniquets may be used, but should be let down to check hemostasis prior to closing the wound. Hemovacs are used when indicated and have not been a source of any difficulty.

Procedures and Complications

Since 1970 42 orthopedic reconstructive procedures have been performed on 32 patients. All patients were severe hemophiliacs, 28 being Factor VIII deficient and 4 Factor IX deficient. The indications for surgery were arthropathy in 23 cases, synovitis in 4 cases, contracture in 6 cases, hemophilic pseudotumor in 4 cases, fracture in 1 case and miscellaneous indications in 4 cases. The procedures are outlined in Table II. The complications are listed in Table III.

Two procedures were complicated by postoperative hemorrhage and infection and another by an infection not associated with hemorrhage. There were three minor postoperative bleeding episodes which did not impair the outcome or prolong the convalescence. These will be discussed in detail in the next section.

Discussion

Arthropathy

The arthropathy of hemophilia is discussed in detail in the previous paper. The knee is most often affected and frequently responds to physiotherapy or splinting. However there are several problems that may require surgical intervention. Among these are severe painful arthropathy or deformity that does not respond to conservative modalities and persistent pain or bleeding associated with signs suggestive of an internal derangement. When total knee replacement surgery is proven reliable and durable it will undoubtedly be the operation of choice for hemophilic arthropathy of the knee. At the present time there are several factors that must be considered. Most hemophilics, despite their disability, lead an active life that puts more stress on their joints than that of the rheumatoid or elderly osteoarthritic patients. The osteoporosis of disuse, muscle atrophy, joint fibrosis and severe deformity may complicate the picture. At the present time we are limiting total knee replacement surgery to those patients who are unable to walk without crutches or who are limited to wheelchairs because of pain, bleeding or deformity. Because of our conservative approach only one total knee replacement has been performed in a 34-year-old patient and the result is satisfactory with relief of pain, a range of motion slightly past 90 degrees and the

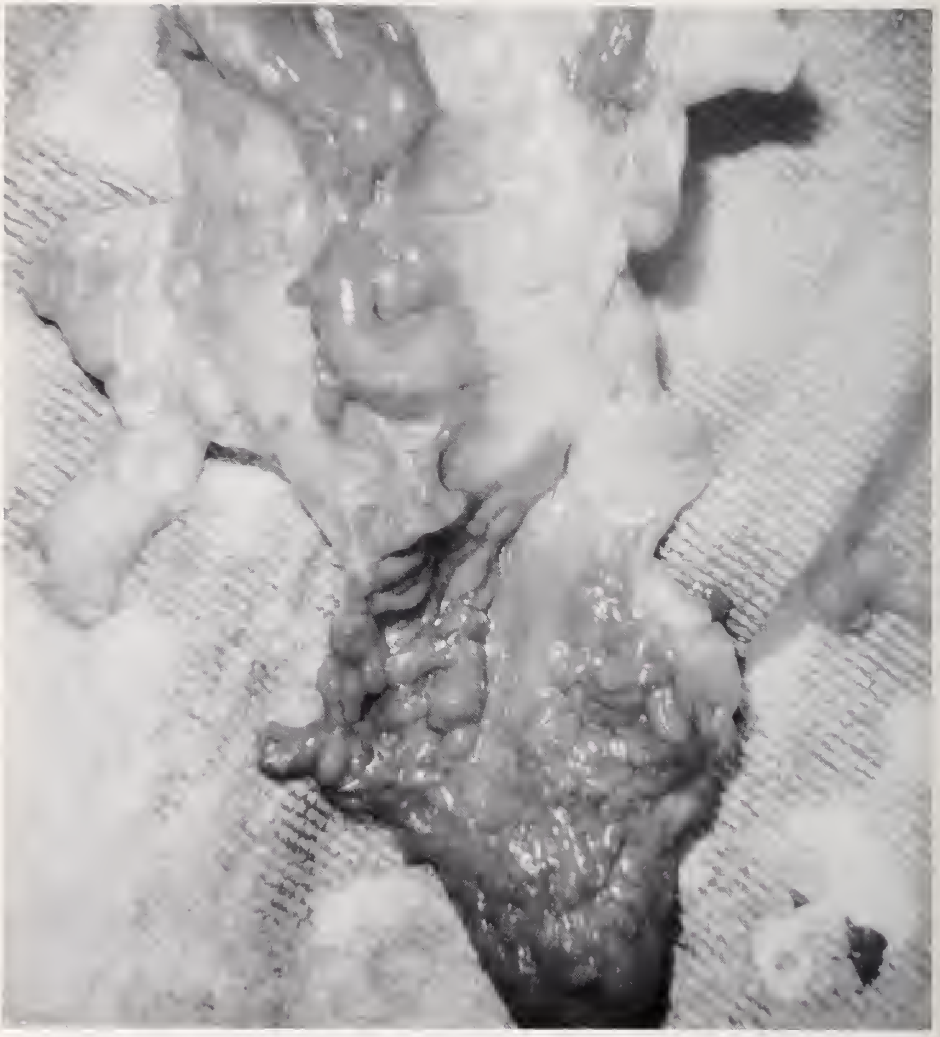

FIG. 1. Medial meniscus with hemorrhage and synovial overgrowth.

ability to walk without support. Six osteotomies were performed about the knee because of deformity. A distal femoral osteotomy with ASIF condylar plate fixation for valgus deformity following fracture healed without complication. Two valgus and one varus proximal tibial osteotomies were performed for pain and deformity. Pain relief and correction of deformity were excellent. All of these patients regained their preoperative range of motion. In two advanced cases proximal tibial and distal femoral osteotomies (as described by Benjamin (2)) were performed. In one of these cases a patella realignment was added to the procedure. The latter case was complicated by severe postoperative hemorrhage into the wound and soft tissues of the anterior compartment. This required decompression of the wound and anterior compartment and infection subsequently set in. Anesthesia below the lower third of the tibia and fibrosis of most of the anterior compartment muscles resulted. Delayed grafting was required to close the wounds. The osteotomies healed three months after surgery and six months following surgery the patient regained a range of motion from 10 to 55 degrees with recurrence of 15 degrees of the valgus deformity. This patient was a known addict and admitted to infusing heroin directly into his intravenous tubing. The part played by heroin in potentiating bleeding and contamination by the injections may have contributed to these complications.

Despite significant arthropathy one occasionally sees localized clicking, locking, tenderness and bleeding at the knee which is suggestive of an internal derangement. Four knees were explored after failure to respond to three to six months of conservative care (Fig. 1). In three, severely deformed meniscii were found and in another several loose cartilagenous bodies were removed. All four patients had relief of their symptoms and this procedure with limited goals should be considered in selected cases.

Arthropathy at the hip is much less common than the knee but when present it does not respond well to nonsurgical modalities. Five total hip replacements have been performed and all have done well (Figs. 2 and 3). All regained a painless range of motion to 90 degrees and were able to walk without external support. Similarly, arthropathy at the elbow does not respond to bracing or physiotherapy. Radial head resection and partial synovectomy has proven useful and the results of this procedure are reported elsewhere in this monograph (Fig. 4).

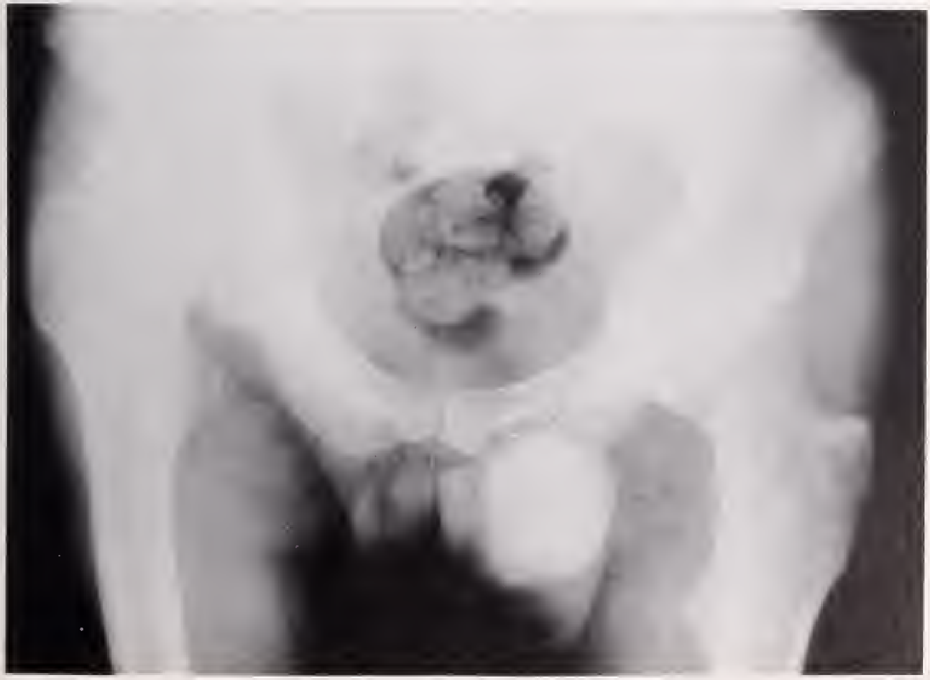

FIG. 2. Advanced hemophilic arthropathy right hip.

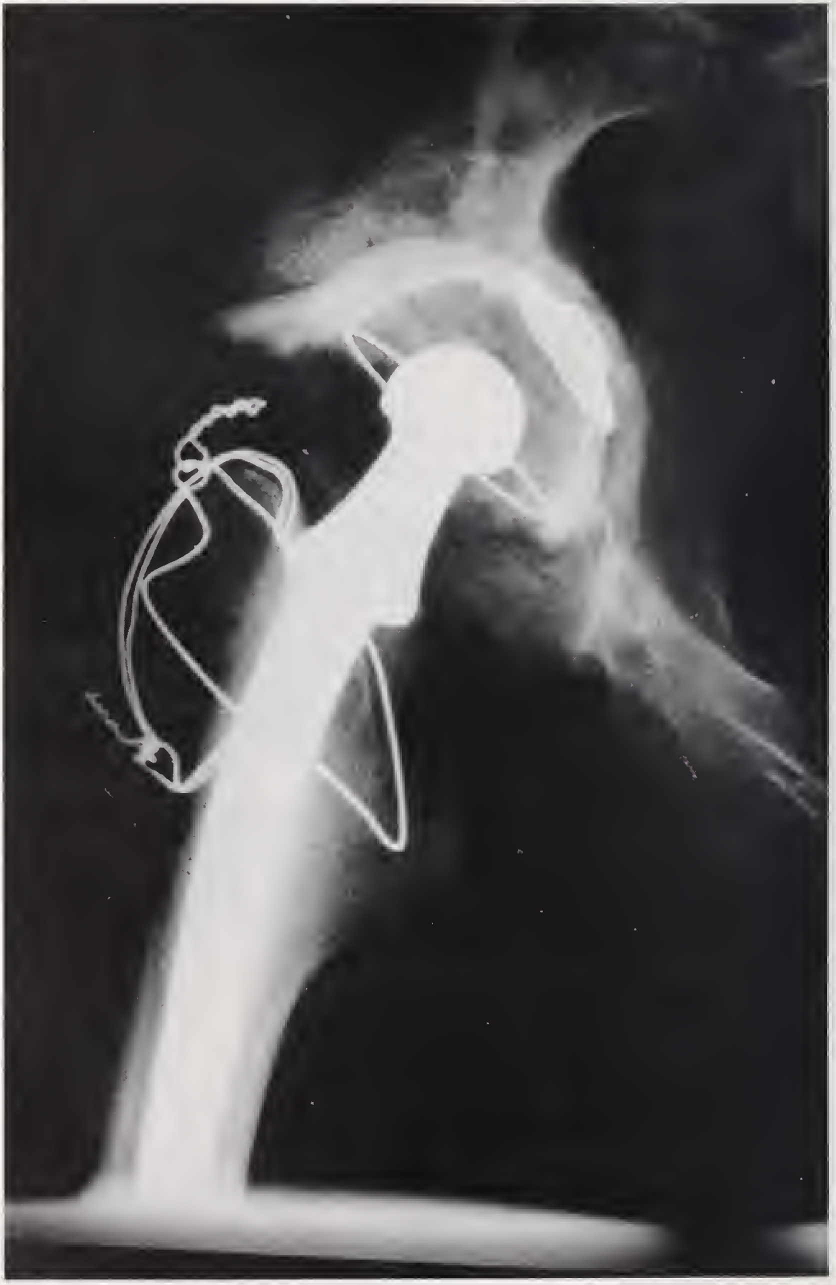

FIG. 3. Same patient—post total hip replacement.

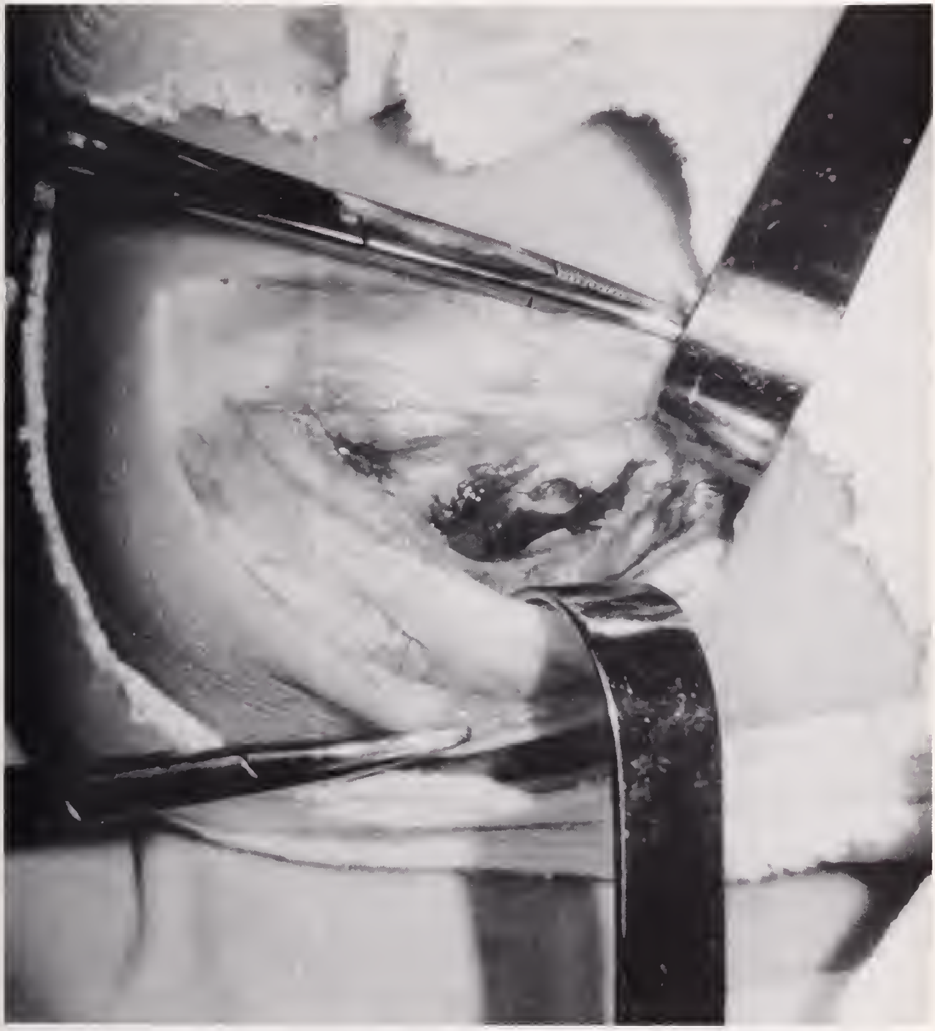

FIG. 4. Hemophilic arthropathy of elbow with extensive synovitis.

Synovitis

The etiology and treatment of hemophilic synovitis especially about the knee remain problematic. Storti et al (3) introduced synovectomy for control of hemorrhage. His results have not been reproduced at many other hemophilic centers and we have reserved this operation for persistent synovitis that has caused severe ligamentous or patella laxity. In three patients synovectomy was performed (Fig. 5). The synovitis was controlled but, despite intensive physiotherapy and early manipulation under anesthesia, motion was lost in all cases. At best, one can expect to regain only 90 degrees of flexion. One patient had synovitis associated with a chronic dislocating, arthritic patella (Fig. 6). In an attempt to maintain motion, a patellectomy was performed and a synovectomy delayed. The synovitis disappeared after four months and the patient has done well with only rare bleeding episodes, a 10 degree extension lag, and flexion to 110 degrees.

Contractures

Contracture is frequently associated with arthropathy and osteotomy, as well as tendon lengthening, may be performed. A tendo-achilles lengthening and a flexor tendon lengthening at the wrist have been performed at this clinic. Equinus contracture at the foot and ankle were corrected in four patients by Lambrinudi triple arthrodesis. All patients had good correction of their deformity (Figs. 7 and 8).

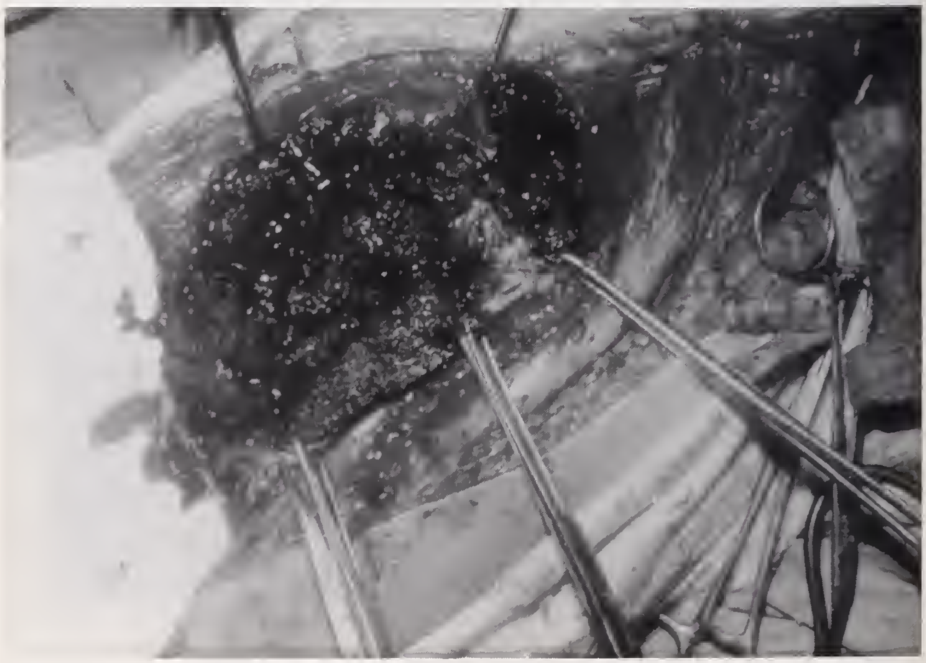

FIG. 5. Hemophilic synovitis of the knee.

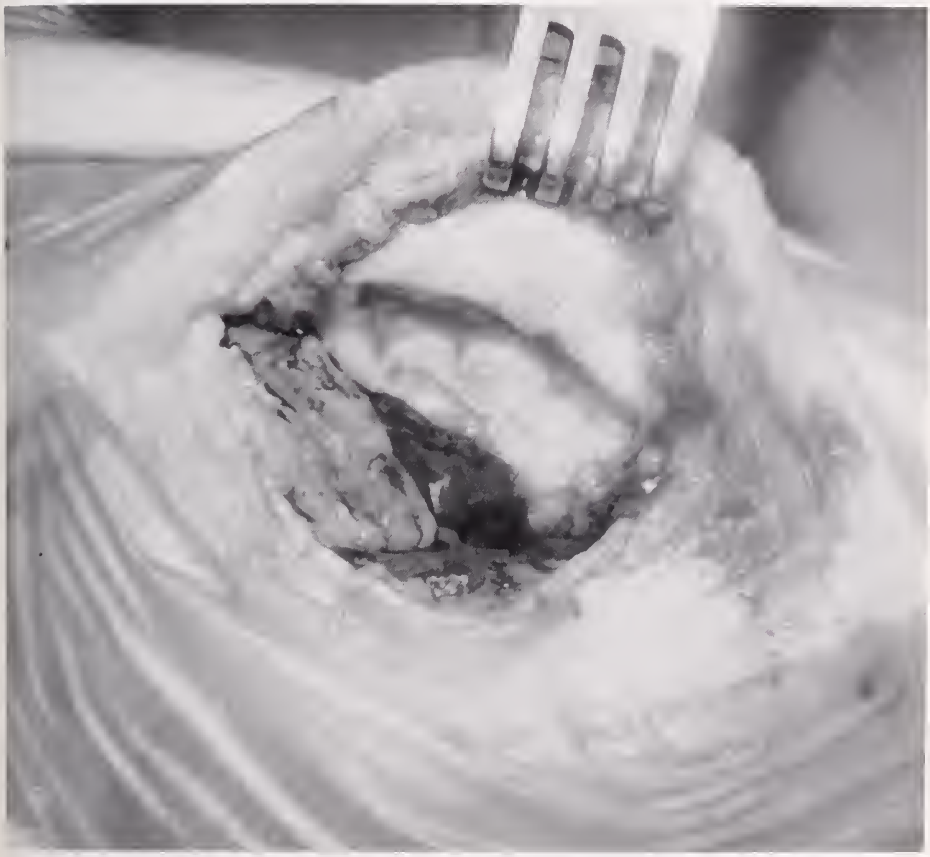

FIG. 6. Hemophilic arthropathy of knee with severe patello-femoral involvement.

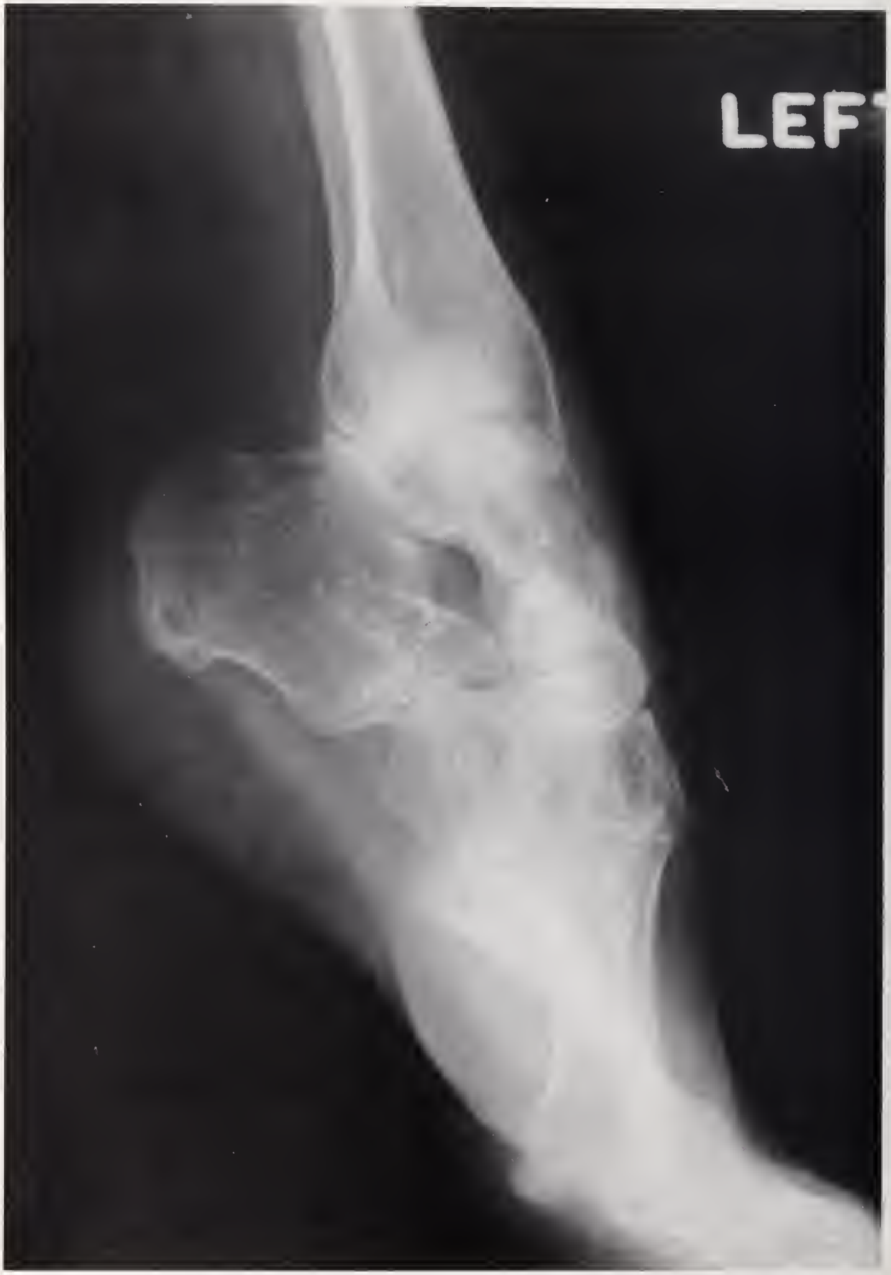

FIG. 7. Severe equinus contracture.

Neuropathy

Nerve entrapment secondary to hemorrhage has been reported and surgical release may be required. Once diagnosed the requisite preoperative tests should be performed. By the time they are completed one can make a decision as to whether the neuropathy has responded to conservative care or whether it will require surgical intervention. We have had several entrapment syndromes but none have required surgical intervention.

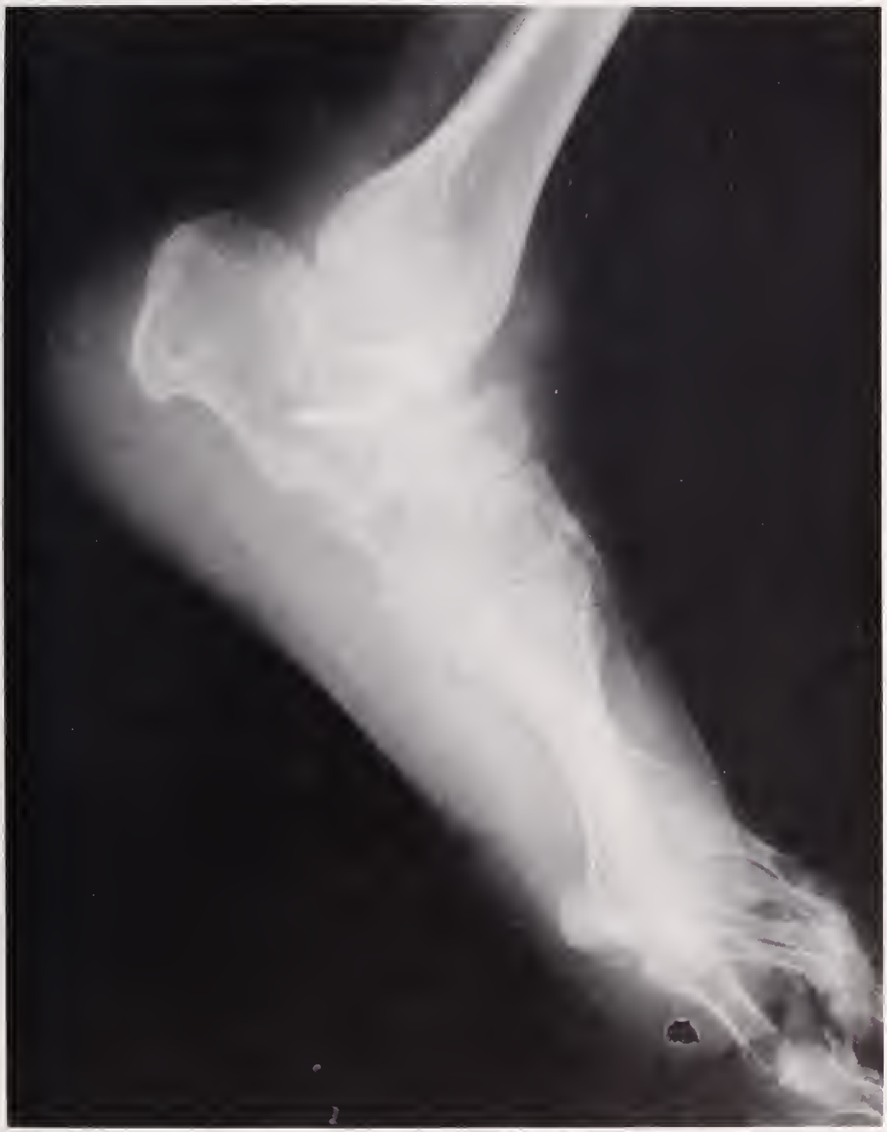

FIG. 8. Same patient following correction by Lambrinudi triple arthrodesis.

Hemophilic Pseudotumor

The treatment of hemophilic pseudotumors has been discussed in detail elsewhere (4, 5). Amputation should be limited to those cases that are not amenable to resection or reconstruction. An above knee amputation was performed for a femoral pseudotumor that had destroyed most of the femur and knee and had broken through the skin. There was osteomyelitis and reconstruction was not possible. A pseudotumor of the femur and a pseudotumor of the buttock were resected without undue difficulty. The wounds healed per primum and no recurrence has been noted after five years and one year, respectively. A large iliac pseudotumor was seen in a 26-year-old patient. It had been present for over 10 years and large masses in the abdomen and buttock were noted. The abdominal mass was palpable to the midline and to the level of the umbilicus (Fig. 9). There was extensive destruction of the ilium and there was a complete femoral neuropathy. Complete surgical removal was not possible because of ureteral and vascular proximity. A large cavity persisted that could not be obliterated, but the wound was closed over hemovac drains. In the recovery room, severe hemorrhage ensued and the patient was returned to the operating room where the abdominal wounds were packed open. Hemorrhage was eventually controlled but infection ensued and only after many weeks was it brought under control. The buttock wound granulated in and healed secondarily, but a persistent anterior sinus was present six months after surgery. Because of this experience, it is our opinion that if a pseudotumor of the large bone is recognized early, resection should be strongly considered.

Fractures

The indications for surgery in fractures is similar to that in the nonhemophiliac. Long periods of cast immobilization will only contribute to further stiffness and osteoporosis and should be avoided if possible. One patient with an intracapsular fracture of the hip had a closed reduction and fixation with a Smith-Petersen nail and plate. Six months after fracture there was complete healing without evidence of avascular necrosis.

Complications

Severe complications which adversely affected the surgical outcome were encountered in only two patients. Hemorrhage and infection in a double osteotomy of the knee and iliac pseudotumor are discussed in detail above. There were two minor soft tissue hemorrhages in patients following total hip replacement. One occurred seven days following surgery when an uncooperative patient insisted on walking without his crutches. Another superficial bleed occurred on the tenth postoperative day. Both responded to rest and replacement therapy. One patient had a painful hemarthrosis following synovectomy and this delayed physiotherapy for approximately one week. One patient had a superficial infection of the lateral wound following a triple arthrodesis. It responded to minor local debridement and antibiotics.

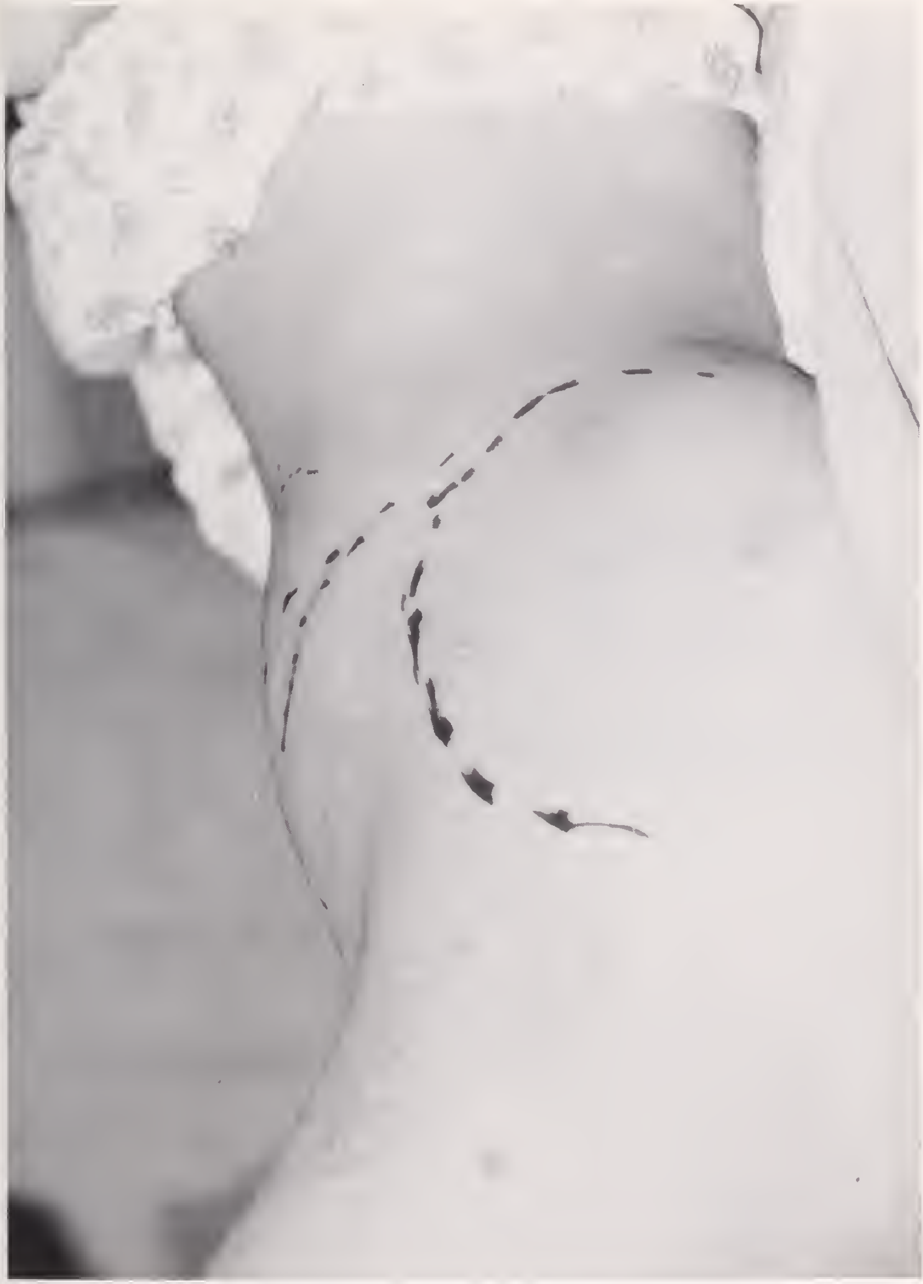

FIG. 9. Extensive iliac pseudotumor.

No patient developed an inhibitor before discharge from the hospital. One patient was noted to have an inhibitor four years following surgery. He was an uncooperative patient and had not returned for followup during the interval. He claims that he did not receive any treatment during this interval and the inhibitor formation may be related to the factor he received for the surgery. He claims that he had not had a single bleeding episode during this four-year interval.

Hepatitis developed in one patient and responded without complications. This occurred in the patient who had resection of the large iliac pseudotumor. No thromboembolic episodes were noted in the patients receiving Factor IX replacement. Hemolysis is discussed in detail in the article by Dr. Aledort.

Summary

Forty-two major orthopedic reconstructive procedures were performed in 32 patients. The orthopedic indications and management are discussed. Close cooperation within the hemophilia team and attention to the details of management can result in a relative low complication rate.

References

1. Post, M. and Telfer, M. C.: Surgery in Hemophilic Patients, J Bone Joint Surg 57-A:1136–1145, December 1975.
2. Benjamin, A.: Double Osteotomy for the Painful Knee in Rheumatoid Arthritis and Osteoarthritis, J Bone and Joint Surg 51-B:694–699, Nov. 1969.
3. Storti, E., Traldi, A., Tosatti, E., and Davoli, P. G.: Synovectomy, A New Approach to Hemophilic Arthropathy, Acta Haemat 41:193, 1969.
4. Ahlberg, A. K. M.: On the Natural History of Hemophilic Pseudotumor, J Bone and Joint Surg 57-A:1133–1135, Dec. 1975.
5. Gilbert, M. S.: Haemophilic Pseudotumor, *Handbook of Haemophilia*. Excerpta Medica, Amsterdam 1975, p. 435–446.

The Mount Sinai Journal of Medicine
Vol. 44, No. 3, May-June, 1977
Printed in U.S.A.

Hemophilic Arthropathy in the Elbow

MARVIN S. GILBERT, M.D. and KENNETH S. GLASS, M.D.

Hemophilia is a disease entity that has been known for over 3,000 years. It was not until the nineteenth century that the association of chronic intraarticular bleeding with joint destruction was made (1). Early in the nineteenth century Wachsmuch (1840) and Lange (1851) considered hemophilic arthropathy as a pseudorheumatism. Grandidier in 1870 maintained the supposition that gout or rheumatism were the cause of arthritis in bleeders. Volkman in 1868 first noted that hemarthrosis might occur as a consequence of scurvy or hemophilia, but it was not until Franz Konig of Gottingen in 1892 attempted surgery of the knee in hemophilia that the schema of hemarthrosis with chronic joint changes was elucidated.

At the present time, the most significant disability associated with this coagulation disorder is from bleeding into the musculoskeletal system. The elbow is the second most commonly involved joint. (2) The resultant limitation of motion and pain not only affects the use of the upper extremity but also may make ambulation a difficulty if aids such as crutches are necessary because of arthropathy in the lower estremity.

In 1958 Margaret Swanton demonstrated that the primary site of intraarticular bleeding was the synovium (3). Andrew Weiss noted that the three types of tissue found in the synovial membrane are areolar, adipose and fibrous and that it is the areolar and adipose tissue that make the synovium so susceptible to hemorrhage (4). He noted that the capillaries of these two types of synovial membrane are extremely superficial, often being separated from the joint cavity by only a single layer of synovial cells with delicate tissue matrix. Suter (5) noted that the synovial membrane lacks a base membrane between the cells and subsynovium and the desmosmal junction between the synovial cells. The cells themselves are often polarized with the nuclei of the endothelial lining cells being located distally from the synovial membrane and the thin attenuated portion of the cell being located nearest the joint cavity. Astrup and Sjolin (6) found the synovial tissue to be almost completely devoid of tissue thromboplastic activity. Hence, hemorrhages into the joint must be controlled almost exclusively by coagulation via the intrinsic pathway. Intrinsic coagulation being defective in hemophilia A and B, bleeding into the joints is prolonged. Any clot that might be formed is lysed by the conversion of plasminogen to plasmin. These factors may help explain why hemophilics have frequent and prolonged hemarthroses.

Swanton (7) noted that the earliest evidence of bleeding consists of small hemorrhages into the synovial and subsynovial tissue. These hemorrhages

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From the Department of Orthopaedics, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029

Requests for reprints should be sent to: Marvin S. Gilbert, M.D., 1100 Park Avenue, New York, N. Y. 10028.

may rupture into the joint space after forming discrete hematomas. In the synovium the hemorrhages may initiate an acute inflammatory response. Following this the deposition of hemosiderin pigment within the synovium is noted. The synovium then hypertrophies with increased·vascularity and cellular infiltration. There is also an increase of type B cells responsible for increased synovial fluid. With continued hemarthoses there is fibrosis and thickening of the areolar and adipose tissues. Cartilagenous and osseous changes seem to occur at a later time. This could be mediated through enzyme changes which are responsible for the synovial inflammatory reaction or through the direct deposition of iron within the cartilage cells or matrix.

We have noted the predisposition of the hemophilic synovium to take part in the initiation of the inflammatory response. Whether this inflammatory response is responsible for cartilaginous breakdown remains to be answered. Hilgartner (8) thinks that this step is enzyme related. Granda, Ranawat and Posner (9) studied the relative enzyme levels of betaglucuronidase cathepsin D and acid phosphatase in the rheumatoid arthritis patient. Ranawat noted that cathepsin D levels are most reliable in assessing synovectomy in rheumatoid arthritis. (He notes that cathepsin levels were significantly elevated in other inflammatory joint diseases.) These values could also be correlated with the severity of the disease. Granda has shown that levels of cathepsin D and acid phosphatase approach those seen in other inflammatory responses, and Dinele (10) has shown that cathepsin D is capable of destroying cartilage in tissue culture. Oronsky (11) reported that human leukocyte in physiologic bufferin ph and fixed aggregate human gammaglobulin release proteases which are capable of degrading the noncollagenous chondromucoprotein matrix of cartilage. He further noted that these lysosomal constituents are released when human leukocytes phagocytose or attempt to phagocytose immune complexes. Movar noted that polymorphonuclear proteases convert bradycarnogin to bradykinin, a substance which increases the vascular permeability pain and swelling of synovium. This is an interesting thought in the pathogenesis of problems in the hemophilic joint.

Weissman (12) suggested that it is the escape of the granular contents from the lysosomes that is sufficient to account for the proliferative and degenerative change seen in clinical and experimental arthritis. Extracts of leukocyte lysosomes were injected into the joints of rabbits while the contralateral was injected with insaline. Within 24 hours of lysosomal injection, an intense inflammatory response occurred, the synovial cells became hypertrophic and hyperplastic. It was Weissman's contention that the substance in the lysosomes may mediate the final common pathway in rheumatoid and inflammatory diseases.

Conservative Care and Surgical Indications

As previously noted, the elbow is the second most common site of arthropathy in the hemophiliac. Changes occur insidiously because it is not a weight-bearing joint, and early limitation of flexion and extension do not interfere with function. With recurrent hemorrhage, increasing limitation of pronation and supination is noted and pain may become an important factor. Late changes may cause significant instability and a tardy ulna nerve palsy. Radiologically, one sees loss of the cartilagenous joint space and subchondral irregularity (Fig. 1). Enlargement of the proximal radial epiphysis is seen quite early. It is hypothesized that this epiphyseal enlargement is due to the hyperemia associated with the recurrent bleeding episodes. It is this enlarged and irregular radial head that eventually causes the severe limitation of pronation and supination. Later changes include cyst formation and occasional mild osteophyte formation. In the advanced arthropathy, the olecranon notch may become enlarged as the humerus seems to erode down through the ulna (Fig. 2).

Once this arthropathy has developed it is very difficult to treat. The mainstay of care is early replacement of the missing clotting factor and prevention of these changes. If a painful hemarthrosis develops it should be splinted for a few days either with a posterior plaster splint or with a sling. Gentle range of motion exercises are begun as soon as the hemarthrosis begins to resorb and the patient is then gradually returned to normal activity. Unlike joints in the lower extremity, the elbow does not respond to attempts at physiotherapy or bracing. Therefore, the changes that occur are permanent. Several patients were noted to have recurrent bleeding despite good hematologic control and many were noted to have pain on motion where

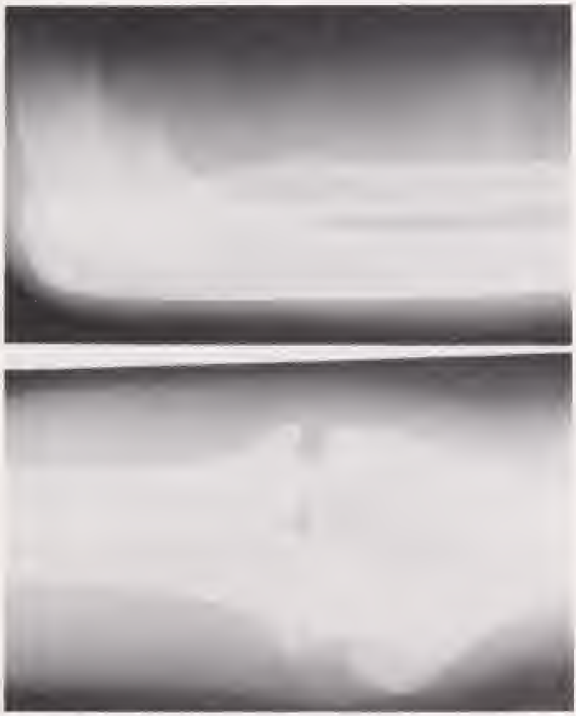

FIG. 1.

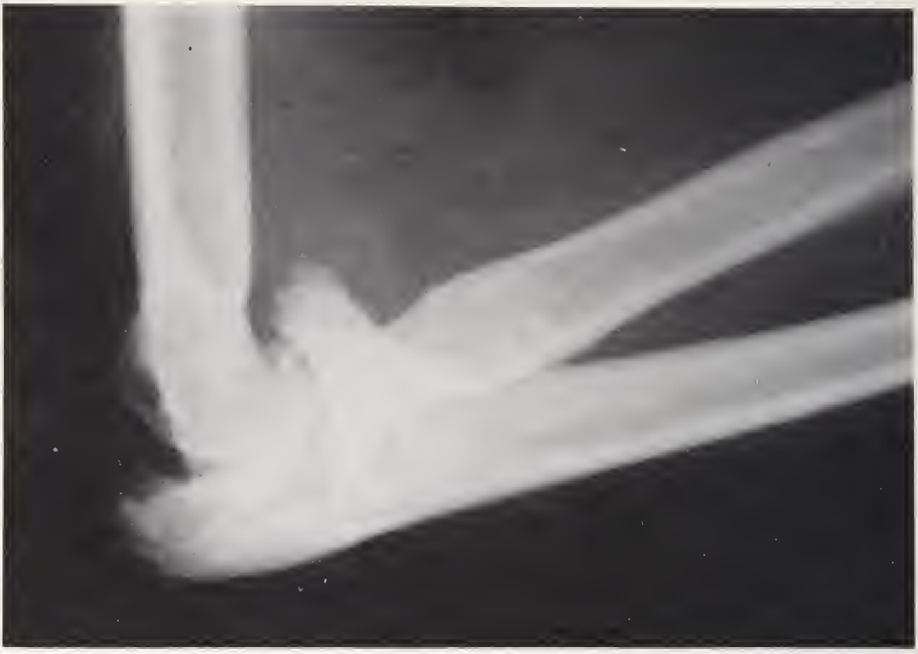

FIG.2.

the enlarged radial head articulated with the humerus. Consequently, we felt that arthrotomy and radial head resection might be indicated. Indications for surgery at the present time include:

1. Recurrent hemorrhage unresponsive to prophylactic factor replacement.
2. Chronic unremitting pain at the elbow associated with tenderness at the radial humeral junction or pain and crepitus on pronation and supination.

We did not feel that fusion of the elbow was applicable as an acceptable alternative to our patients. We also did not feel that total elbow replacement was a feasible alternative at the present time for this patient group. Therefore, we elected to perform a limited synovectomy and radial head resection.

Operative Technique

The general hematologic and orthopedic considerations for surgery in the hemophiliac are considered elsewhere in this journal. General anesthesia and a tourniquet were used for this procedure. A lateral incision was made extending from just proximal to the lateral epicondyle distal toward the ulna. The interval between the anconeus and the extensor carpiulnaris was separated. The arm was kept in pronation and the supinator was retracted. The joint capsule was then incised and bulky hemosiderin laden synovium was encountered. This was dissected from the undersurface of the capsule. Following this the radial head was removed just below the neck. More synovium was then encountered and as much as possible was removed from the joint. A rongeur can be helpful. We did not dislocate the joint as we did not want to risk further limitation of motion. In no case did we make a radial incision to complete the synovectomy as we felt that most of the pathology centered about the radial humeral articulation. The wound was then closed in serial layers after the tourniquet had been let down. Postoperatively the elbow was placed in a splint for seven to fourteen days after which active range of motion was begun (Figs. 3 and 4).

Results and Discussion

Seven patients underwent the surgical procedure. All were evaluated by the authors one and a half to four years postoperatively. All wounds healed per primum without infection. In all cases, factor replacement was maintained for at least two weeks. In four of the cases a third week of lower levels was maintained when mobilization was begun. The results are tabulated in Table I.

Storti and Ascari (13) reported on their experience with 63 surgical synovectomies in 54 hemophiliacs. This included 51 synovectomies of the knee, 3 of the elbow and 1 of the ankle. Storti noted that only his results in the knee were satistically significant and made the following observations. In 94% there was a marked reduction in the number of hemarthroses with 60%

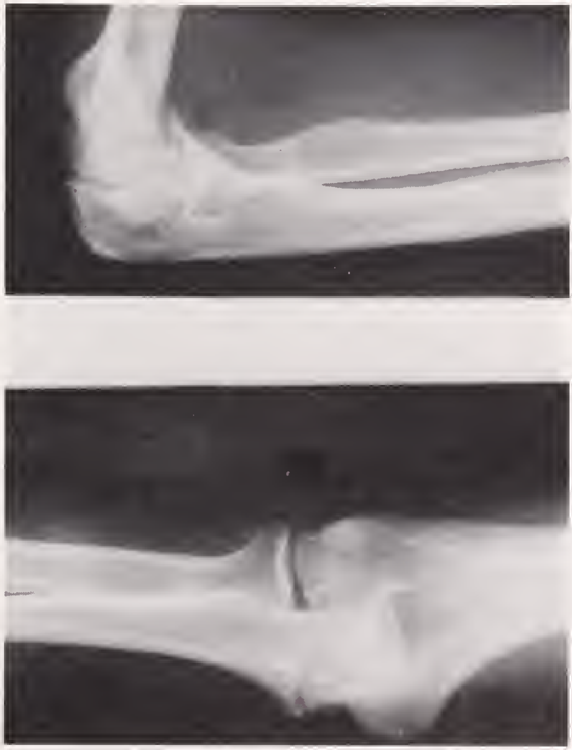

FIG.3.

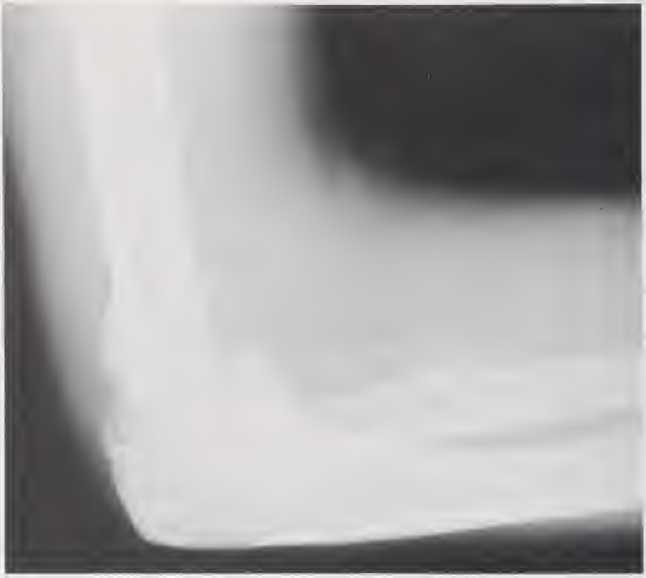

FIG.4.

TABLE I

Results

Cases	Elbow	Follow up -M-	Preop *Ext* Flex	Preop Sup/ Pron	Postop *Ext* Flex	Postop Sup/ Pron	Comment	Pain Relief
1 C. C.	L	36	−20/95	None	−20/145	45/45	Unstable postop necessitating splinting	Good
2 P. S.	R	48	−35/130	15/15	−40/140	65/90	No rebleeding	Good
3 J. Y.	R	20	−45/135	45/45	−25/100	45/45	Rebleed was noted after surgery	Fair
4 R. A.	L	24	−20/110	10/30	−20/110	25/35	Good result	Good
5 H. J.	L	48	−6/20	30/10	−30/140	50/90	Good result	Good
6 R. D.	R	28	−10/130	30/30	−40/110	30/30	Postop rebleed	Fair
7 B. S.	R	18	−27/120	45/45	−20/120	45/45	Postop rebleeding after 1 year	Fair

noting complete cessation. Twenty-eight percent noted occasional mild pain. The joint mobility was improved in 55%, unchanged in 33% and deteriorated in 12%. Other authors have subsequently reported a decrease in the number of hemarthroses following synovectomy. William Arnold (14) noted that the procedure is not entirely benign. The hypothesis of decreased enzyme activity secondary to surgical synovectomy and the secondary protection of the cartilage seems inviting, but the synovium may regenerate and the disease continue. However, he does note that when pseudohemangiomatous transformation of the synovium occurs, synovectomy may be the procedure of choice.

There are no specific reports about synovectomy at the elbow. However, this procedure has been utilized in other disease entities. Inglis (15) noted significant relief of pain and increased range of motion in his series of synovectomies done for rheumatoid arthritis. Torgerson (16) noted synovectomies for rheumatoid arthritis of the elbow gave relief of pain in all his cases. Marmor (17) in a similar series of synovectomies and radial head excisions noted significant relief of pain in all of his cases with increased range of motion in half.

In our small series, the following observations could be made. In only four of seven cases was there marked diminution of recurrent hemorrhages. Five of the seven noted significant long-term pain relief with an additional case noting partial pain relief. The range of motion was increased in three patients, decreased in one and unchanged in three. Instability was noted in one patient postoperatively but this responded to splinting for two weeks. This patient had advanced hemophilic arthropathy with deep erosion into the olecranon notch and we feel that if at all possible the procedure should be done before the arthropathy is this advanced.

Conclusions

In conclusion, we have a limited experience with a small number of patients. The procedure of partial synovectomy and radial head resection is one of the few procedures we have available for arthropathy at the elbow which has failed to respond to conservative methods. We did not consider total joint replacement in our patients as it is an experimental procedure at the present time and synovectomy and radial head resection is a relatively safe, well tolerated procedure that does not rule out total joint replacement in the future. We noted improvement in symptoms in 50% of our cases. In selected cases which do not respond to conservative care we feel that this procedure should be considered.

References

1. Konig, F.: Diseases of Joints in Bleeders, Clin Ortho 52:5, 1967.
2. Koch, K.: Clinical Manifestations of Hemophilia. Musculoskeletal Disorders of Hemophilia, Natl Acad Sci 1973.
3. Swanton, M. C.: The Pathology of Hemarthrosis in Hemophilia. In Hemophilia and Hemophiloid Diseases. University of North Carolina Press, Chapel Hill, N.C., 1957, pp. 219–224.
4. Weiss, A.: Hemarthrosis and Hemarthropathy in Hemophilia A and B. Musculoskeletal Disorders of Hemophilia, Natl Acad Sci 1973.
5. Suter, E. R. and Majno, G.: Ultrastructure of the Joint Capsule in the Rat. Presence of (2) Kinds of Capillaries, Nature 201:940, 1964.
6. Astrup, T. and Sjolin, K. E.: Thromboplastic and Fibrinolytic Activity of Human Synovial Membrane and Fibrous Capsular Tissue, Proc Soc Exp Biol Med 97:852–853, 1958.
7. Swanton, M. C.: Hemophilic Arthropathy in Dogs, Lab Invest 8:1269–1277, 1959.
8. Hilgartner, M. W.: Pathogenesis of Joint Changes in Hemophilia. Musculoskeletal Disorders of Hemophilia, Natl Acad Sci 33, 1973.
9. Granda, S. L., Ranawat, C. S., and Posner, D. S.: Levels of 3 Hydrolases in Rheumatoid and Regenerated Synovium, Arth Rheum 14:223–230, 1971.
10. Dinele, J. T.: Aetiological Factors in Collagen Diseases. Lysosomal Enzymes and Degradation of Cartilage Matrix, Proc Roy Soc Med 109–119, 1962.
11. Oronsky, A., Ignarro, L., and Perper, R: Release of Cartilage Mucopolysaccharide-degrading Natural Protease from Human Leukocytes, J Exp Med 138:461–470, 1973.

12. Weissman, G., Spilberg, I., and Rakauer, K.: Arthritis Induced in Rabbits by Lysates of Granulocyte Lysosomes, Arth Rheum 12(2):103–113, 1969.
13. Storti, E. and Ascari, E.: Surgical and Chemical Synovectomy, Ann N.Y. Acad Sci 316–327, 1975.
14. Arnold, W.: Discussion Paper: Synovectomy, Ann NY Acad Sci 338, 1975.
15. Inglis, A., Ranawat, C. S., and Straub, L.: Synovectomy and Debridement of the Elbow in Rheumatoid Arthritis. J Bone Joint Surg 53b:652–662, 1971.
16. Torgerson, W. and Leach, R.: Synovectomy of the Elbow in Rheumatoid Arthritis, J Bone Joint Surg 52b:371–375, 1970.
17. Marmor, L.: Surgery of the Rheumatoid Elbow. J Bone Joint Surg 54a:373–378, 1972.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May-June, 1977
Printed in U.S.A.

Hemophilia: Anesthetic Implications

HATIM HYDERALLY, M.D. AND DAVID C. C. STARK, M.D.

With the continued progress in understanding the mechanism of coagulation of blood and the control of hemorrhage during surgery, the management of hemophilia patients has become greatly simplified. Thus, the anesthesiologist's task has become much easier. For instance, one is less concerned about the possibility of handling such patients successfully now that concentrated factors are available. Nevertheless, hemophilic patients in particular, and those suffering from other coagulopathies in general, must be handled in the full knowledge of the specific defect involved. Since hemophilia surgery is now being done on a regular basis in many centers, it is timely to review the anesthesia problems encountered at The Mount Sinai Hospital over the past six years.

Historically, the only available therapy was fresh blood or the administration of animal antihemophilic globulin (AHG) which could usually be counted upon to arrest the hemorrhage, but could not be administered for long enough periods to make elective surgery feasible. Subsequently, preoperative and postoperative infusion of fresh frozen plasma increased the levels of factor VIII and IX somewhat, but at the expense of producing hemodilution and hypervolemia. In fact, many of these patients had difficulty with high output cardiac failure. With the general availability of factor concentrates, major elective surgery in the hemophiliac patient has now become feasible.

Factor concentrates are administered immediately prior to surgery to raise their level in the blood to a point where coagulation may be confidently predicted (see Aledort). Clearly extreme care should be exercised in the preoperative preparation and handling of these patients. Meticulous attention must be paid to avoiding even minimal trauma. In general, hemophiliacs are intimately familiar with their disorder, cooperative and anxious to help in any way to make surgery easier and safer for themselves. Preoperative medication by subcutaneous or intramuscular routes should be forbidden. Diazepam given orally some one and a half to two hours prior to surgery produces effective sedation and should be satisfactory in most hemophiliac patients (1). In the emergency situation or in the highly nervous and anxious patient, preoperative medication by the intravenous route is to be preferred.

Elective surgery procedures should be performed early in the day to permit recovery from surgery at a time when all ancillary facilities are available for immediate postoperative management (2).

Hemophiliac patients require repeated intravenous infusions in their lifetime, and it is of great importance that their veins be conserved. Venipunc-

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From the Department of Anesthesiology, Mount Sinai School of Medicine of The City University of New York.

Requests for reprints should be sent to: Hatim Hyderally, M.D., Department of Anesthesiology, Mount Sinai School of Medicine, Fifth Avenue and 100 Street, New York, N. Y. 10029.

ture should be carried out with extreme care and only by those experienced in the technique. Cutting down on veins should be avoided wherever possible (2).

Local infiltration and regional anesthetic techniques are not recommended in these patients because of the possibility of producing hematoma. Spinal and epidural anesthesia would be particularly hazardous. Epidural hematomata with neurologic sequelae have been known to follow these procedures in patients receiving anticoagulant therapy (3) and to occur spontaneously (4). Therefore, regional techniques are to be scrupulously avoided in the hemophiliac. Extravasation of blood and formation of a hematoma in deep tissue planes such as intra-oral structures, fascial planes of the pharynx, larynx and trachea and in muscles and joints, presents several problems to the anesthetic management of these patients.

For the simple procedure of short duration, intravenous ketamine might be considered, although there is little record of its use. For other procedures a simple inhalation technique, using a mask, being extremely careful to protect lips, tongue, and pharynx from damage caused by pressure on teeth and edges of an oropharyngeal airway is satisfactory. If endotracheal intubation is necessary, it should be performed with extreme care and gentleness, using a curved laryngoscope, a smaller than usual tube, well lubricated and at a time when the jaw muscles are fully relaxed. The oral route should always be chosen as even the gentlest nasotracheal intubation may result in bleeding. There are a few intra-oral operations that cannot be managed in this fashion, however more convenient it may be, to use a nasal tube.

Blind oropharyngeal suction should be avoided; if oral secretions are present they should be removed by gentle suction under vision, never permitting the mucosa to be trapped in the suction tip.

TABLE I

43 Hemophiliac Patients Undergoing Orthopedic Surgery

Surgical Procedure	No. of Cases	Anesthesia
Synovectomy of elbow and/or excision of radial head	11	Thiopental N_2O/O_2 Halothane
Synovectomy of knee	7	Thiopental N_2O/O_2 Halothane
Manipulation of knee	4	Thiopental Diazepam I.V.
Menisectomy	4	Thiopental N_2O/O_2 Halothane
Tibial and/or femor osteotomy	1	Endotracheal Thiopental N_2O/O_2/Fentanyl/ d-tubocurare
High tibial osteotomy	1	Thiopental N_2O/O_2 Halothane
Lengthening of flexor tendons of hands	1	Thiopental N_2O/O_2 Halothane
Resection of I-P joints of toes	1	Thiopental N_2O/O_2 Halothane
Triple arthrodesis of foot	4	Thiopental N_2O/O_2 Halothane
Charnley low friction arthroplasty of hip	6	Endotracheal Thiopental
Removal of ingrowing toe nail	2	Thiopental N_2O/O_2 Halothane
Exploration of L knee	1	Endotracheal Thiopental N_2O/O_2 Fentanyl d-tubocurare

Extubation should be performed with the same gentleness and in a moderate plane of anesthesia to ensure tranquil emergence. Extravasation of blood into the tongue, floor of the mouth, and fascial planes surrounding the pharynx, larynx and trachea can produce gross swelling dangerously compromising the airway.

Conclusion

Table I reviews the administration of anesthesia for 43 orthopedic surgical procedures in hemophiliac patients over a period of six years. The simpler procedures were performed under inhalational general anesthesia using a mask. Endotracheal intubation was used wherever indicated. The principles of management outlined in this communication were meticulously followed in every case. Over 50% of the patients had chronic elevation of the SGOT and SGPT prior to surgery, but followup testing did not indicate any significant change. One patient developed acute antigen-positive hepatitis two weeks after surgery, but recovered uneventfully. Since no anesthetic complications occurred in any patient, it is concluded that major surgical intervention is now feasible in the hemophiliac patients.

References

1. McCaughey, W. and Dundee, J. W.: Comparison of the Sedative Effects of Diazepam Given by the Oral and Intramuscular Routes, Brit J Anaesth 44:901–902, 1972.
2. Biggs, R. and MacFarlane, R. G.: *Treatment of Hemophilia and Other Coagulation Disorders*. F. A. Davis Co., pp. 130–131, 254–259, 1966.
3. DeAngelis, J.: Hazards of Subdural and Epidural Anesthesia during Anticoagulant Therapy, Anesthesia and Analgesia. Curr Ther Res 51:676–679, 1972.
4. Newberry, J. M.: Paraplegia following General Anesthesia, Anaesth 32:78–79, 1977.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May–June, 1977
Printed in U.S.A.

Radiologic Evaluation of the Hemophilic Hip

STEPHEN TEITELBAUM

The hip, being a relatively rare site of hemophilic arthropathy, has not been studied as extensively as have been the more commonly affected joints (knee, elbow and ankle). Duthie (1) noted only five hemarthroses at the hip from a total of 366 recorded at the Nuffield Orthopaedic Center between 1966 and 1969. Jordan (2) noted involvement of 16 hips in 56 patients with a total involvement of 268 joints. Only three articles (3, 4, 5) dealing specifically with hip arthropathy were located in a search of the literature. Recently, Boone (6) documented that limitation of motion about the hip is not uncommon and Duthie (7) discussed reconstructive surgery. It was therefore timely to examine the radiographic pathology affecting this articulation in the hemophiliac.

Methods

All hip x-rays obtained at the Mount Sinai Hemophilia Center between July 1969 and June 1975 were reviewed and evaluated. Because this was a rare site of hemorrhage and because we were dealing with a young population, the pelvis and hips were not routinely x-rayed. X-rays were only obtained when there was a possibility of pathology as indicated by hemorrhage, pain, limp, or limitation of motion. At the present time we are routinely obtaining x-rays every five years as compared with yearly x-rays of the knees, elbows and ankles. Thirty-four x-rays were available for review (68 hips as a pelvis x-ray was always obtained) from 175 patients. The incidence of pathology is probably high because the clinic has an active Orthopedic Service and many patients are referred specifically for orthopedic consultation.

Results

Twenty hips were evaluated prior to epiphyseal closure and 48 were from the mature skeleton.

Of the 20 hips with open epiphyses, none demonstrated intraarticular pathology. An increase in the femoral neck angle (greater than 140°) was felt to exist in 16 hips, but positioning was not always exact and exact measurements are not reported. Four hips in two patients were felt to be mildly subluxed.

Sixteen mature hips also demonstrated a valgus deformity and four had an angle of less than 120°. One hip was subluxed. Osteoporosis is difficult to evaluate but seven pelvis x-rays showed enough cortical thinning to warrant this designation. One hip demonstrated a cyst in the area of the lesser

Harpur College Volunteer, IHTC, Mount Sinai Hospital, July–August 1975.

trochanter. The nature of this benign appearing lesion is unclear, but it was similar to that of a fibrous cortical defect.

Fifteen hips showed distinct degenerative changes. Four of these were consistent with old avascular necrosis. The other hips manifested varying degrees of narrowed joint space (11), subchondral irregularity (11), femoral head deformity (9), cyst formation (6) and osteophyte formation (6). In eight there was central migration of the acetabulum with thinning of the medial wall of the acetabulum.

Four patients were evaluated for hip fractures during the period of the study. There was an intracapsular fracture which occurred in a normal hip following trauma. Healing occurred after nailing and there was no evidence of avascular necrosis four years later. One patient with avascular necrosis and limitation of motion sustained an intertrochanteric fracture after a fall. It healed following conservative treatment. One of the hips that demonstrated avascular changes had sustained an intracapsular fracture ten years ago which was treated nonoperatively in Egypt. It went on to non-union and total hip replacement was suggested at the time of consultation. A fourth patient had an intracapsular fracture treated five years ago by Austin Moore arthroplasty. The hip was asymptomatic and the x-ray showed good positioning of the prosthesis without sinking or central migration.

Five of the patients with degenerative hips have been treated with Charnley low friction arthroplasties. All are functioning well.

Summary

Sixty-eight hips were examined radiologically in 175 patients. A valgus deformity was noted in many of the younger patients. Four skeletally mature hips demonstrated avascular necrosis and 15 others demonstrated evidence of arthropathy. Four hip fractures were noted, two of which occurred during the study period.

References

1. Duthie, R., Matthews, J., Rizza, C., and Steel, W.: *The Management of Musculo-Skeletal Problems in the Haemophilias*. Blackwell Scientific Publications, Oxford, 1972.
2. Jordan, H.: *Hemophilic Arthropathies*. Charles C. Thomas, Springfield, Il., 1958.
3. Kahn, H.: Manifestations of Hemophilia at the Hip, Radiology 22:286, 1934.
4. Winston, M.: Hemophilic Arthropathy at the Hip, J Bone Joint Surg 34B:412, 1952.
5. Kambuoroglou, G., Mandalaki, T., Lambrou, L., and Krettos, S.: The Orthopedic Problems of the Hip Joint in Haemophilic Patients. Proceedings of IX Congress of the World Federation of Hemophilia, Istanbul, 1974.
6. Boone, D.: Joint Motion in Hemophilia. Results of a Nine Year Followup. Proceedings of the Second International Workshop on Hemophilia, San Jose, Costa Rica, 1975.
7. Duthie, R.: Reconstructive Surgery of the Hemophilic Hip. Presented at the Hip Society, New Orleans, 1976.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May-June, 1977
Printed in U.S.A.

Hemophilia and the Nervous System

SEYMOUR GENDELMAN, MD.

The disease states of hemophilia (factor VIII and IX deficiency) have been known since antiquity although the genetics and pathophysiologic coagulation defects have required centuries to elucidate. The propensity of the illness to affect the nervous system has been well known and a number of reports and reviews on the subject have been presented in the era prior to the development of modern treatment methods (1–15). Since the mid-nineteen sixties and early seventies, various concentrates of factors VIII and IX have revolutionized the treatment of hemophilia (16–23). The daily life patterns, particularly of those patients with severe (less than 1%) or moderate (1–4%) deficiency states, have been greatly altered by the availability of concentrated factors, home therapy and sophisticated training and treatment centers. The present review is an attempt to reevaluate the incidence and prognosis of the neurologic problems encountered in the Hemophilias.

Materials and Methods

All patients enrolled in The Mount Sinai Hospital (New York) Hemophilia clinic from 1964 to the present were reviewed in terms of neurologic involvement. Two hundred and one patients with either factor VIII or IX deficiency were reviewed. Most of the patients with neurologic complications were seen on at least one occasion by the author. Those patients not seen were recorded as having neurologic involvement only if the event and examination was clearly documented in the clinic record or inpatient chart or if appropriate pathologic documentation was recorded.

All patients had documented assay of deficient factor levels.

Total neurologic review of patients and complications was recorded which roughly reflects the era of availability of concentrated hemophilic factors.

Results

Two hundred and one patients were reviewed. Twenty-eight patients had factor IX deficiency (Hemophilia B) and 173 patients had factor VIII deficiency (Hemophilia A). All neurologic complications in the present series were in patients with severe hemophilia.

In the entire series, 51 patients had 1 or more neurologic complications comprising 89 complications. There were 56 central nervous system and 33 peripheral nervous system complications (Table I). Three craniotomies were performed in this series, twice for intracranial hemorrhage (subdural hema-

From Department of Neurology and International Hemophilia Training Center, The Mount Sinai Hospital, New York, N.Y. 10029

Requests for reprints should be sent to: Seymour Gendelman, M.D., 111 East 88 Street, New York, N.Y. 10028.

TABLE I

Nervous System Involvement in 201 Patients with Hemophilia

There was an incidence of 14.9% central nervous system involvement and 12.9% involvement of the peripheral nervous system.

Central Nervous System – 14.9% incidence	
Subdural Hematoma[1]	5
Subarachnoid hemorrhage	22
Intracerebral hemorrhage[2]	14
Brain Stem hemorrhage	2
Seizure disorder	9
Probable vascular occlusion	2
Neoplasm[3]	1
Spinal cord	1
	56
Peripheral Nervous System – 12.9% incidence	
Sciatic nerve	2
Femoral nerve	16
Peroneal nerve	2
Lumbosacral radiculopathy or plexus[4]	2
Median nerve	5
Ulnar nerve	3
Radial nerve	2
Misc.[5]	1
	33

[1] Surgical intervention in one instance.

[2] Three deaths in this group. One surgical intervention without death.

[3] Convexity meningioma with uneventful surgical excision.

[4] Retroperitoneal hemorrhage with probable involvement of lumbosacral plexus. Second episode probable discogenic without evidence of hemorrhage.

[5] Superficial temporal artery aneurysm secondary to trauma. Excised uneventfully.

toma and intracerebral hemorrhage) and once for uneventful excision of a convexity meningioma (24). There were 3 deaths, all secondary to intracerebral hemorrhage.

Average age of all patients was 30.1 years. Central complications occurred at an average of 20.6 years and peripheral problems at an average age of 27.0 years. Complications with factor IX deficiency occurred at a slightly greater age but its significance is doubtful because of the small number of cases of hemophilia B.

The incidence of total neurologic involvement in the patients with hemophilia was 25.4%. Patients with central and peripheral problems accounted for 14.9% and 12.9%, respectively. Fourteen patients had multiple complications, the most conspicuous being in 2 patients with 5 complications each (mixed central and peripheral). One patient had 3 separate episodes of iliac hemorrhage and resulting femoral neuropathy. Two patients had 3 or more subarachnoid hemorrhages and one patient had 2 intracerebral hemorrhages. The most unusual cases occurred in a patient with Hemophilia B who presented with a transient aphasic episode as his first manifestation of convexity meningioma and a patient with Hemophilia A who developed a superficial temporal artery aneurysm following local trauma. Both instances were studied fully, including angiography and subsequent surgery with appropriate factor coverage.

The most common syndromes encountered were subarachnoid hemorrhage, intracerebral hemorrhage and femoral neuropathy. Subarachnoid hemorrhage followed trauma in 9 instances, was spontaneous in 8 instances and its relationship to trauma unknown in the other 5 instances. In intracerebral hemorrhage, there was a slightly greater relationship to trauma, occurring in 8 instances and occurring spontaneously in 4 instances. In 2 instances the relationship to trauma was unknown. Seizure disorder usually arose in conjunction with or as an outcome of intracerebral or subarachnoid hemorrhage. In one instance, seizures appeared spontaneously and in another instance occurred in relationship to a convexity meningioma.

The relationship of trauma to femoral nerve injury (following hemorrhage into the iliac muscle) was much less certain, a history of definite trauma being obtained in only four, instances leaving a distinct impression of predominant spontaneous occurrence.

Discussion

The incidence of peripheral nervous system involvement in our hemophiliacs of 12.9% is certainly consistent with that of a prior period (7). The incidence of 13.8% involvement in the same clinical population (in the same hospital) is almost identical—showing that a significant change either in incidence or area of involvement has not occurred. The prognosis is much the same with perhaps a slightly reduced morbidity as a result of prompt recognition of deficit and appropriate quantitative factor administration. Most patients recovered uneventfully and were able to return to their usual level of functioning in distinction to the degree of impairment following repetitive joint damage from hemarthrosis. The greatest areas of morbidity occurred following intracerebral hemorrhage, often with residual hemiparesis and subsequent seizure disorder.

Our incidence of 14.9% central nervous system involvement is somewhat higher than the usual average incidence of approximately 10%. This may be in part because of the presence of the Mount Sinai Hemophilia Clinic serving as a center for such patients. It may also reflect our awareness that even a relatively minor head trauma event is a potentially life-threatening situation in the hemophiliac (25–27). Thus head trauma is an indication for immediate vigorous treatment, particularly in the severe hemophiliac.

The distribution of the various anatomic levels of involvement is not unique for the hemophiliac but simply a reflection of their bleeding tendency.

Prompt recognition of the anatomic nervous involvement, rapid adequate administration of the deficient factor, removal of further trauma and appropriate physical restriction will usually result in minimum deficit. In appropriate situations, diagnostic approach via invasive routes can be performed in the hemophiliac just as in the normal as long as appropriate concentrate or factor is administered and no inhibitor is present. Similarly, appropriate surgical procedures may be performed (28–30).

Commonest Clinical Nervous System Syndromes

1. *Femoral Neuropathy secondary to iliacus muscle hemorrhage.* This is the most common peripheral nerve injury encountered in the hemophiliac (7, 11). The syndrome usually begins with groin pain, at times radiating to lumbar or anterior thigh musculature. It may begin insidiously, usually reaching a maximum in hours to 3-4 days but may require weeks. Though trauma may often be present, in our experience, symptoms more often begin spontaneously.

The hip is held in flexion with slight lateral rotation and forcably resists extension. With the hip flexed, the patient may allow medial or lateral rotation but prefers to lie on the affected side with both thighs flexed.

A mass may be palpated in the lower abdominal quadrant of the affected side. The inner iliac groove is usually difficult to palpate and may be made more difficult to do so by the patient's persistence to maintain hip flexion. Ecchymosis is not usually seen but anemia may become apparent.

Femoral nerve involvement usually but not necessarily follows the pain. Cutaneous hypesthesia, reflex change and paresis of hip flexion and knee extension are the most common findings.

The hypesthesia involves the anterior thigh and extends below the knee involving the anterior medial one third of the leg than tapering as far as the medial malleolus. The knee jerk is usually diminished to absent. Recovery occurs slowly and spontaneously, usually abetted by bed rest and deficient factor replacement with ice packs over the region of the groin. Full recovery of the femoral neuropathy may take up to 6–8 months. With incomplete recovery, quardriceps wasting may be present but more often residual hypesthesia about the knee remains. Though distinctive this syndrome is not limited to hemophiliacs (7, 31, 32).

2. *Subarachnoid hemorrhage.* Subarachnoid hemorrhage (SAH) may be spontaneous or related to trauma. By definition, there is no penetration of blood into central nervous tissue which accounts for the better prognosis of this syndrome as compared to intracerebral hemorrhage (33, 34, 35).

The initial complaint is usually headache followed by stiff neck, often with diminished level of consciousness and the appearance of meningeal signs. Variation in time of onset is related to the association and severity of precipitating trauma.

Any persistent, unexplained headache of more than 4–8 hours duration must evoke suspicion of intracranial hemorrhage and warrants factor replacement therapy, neurologic examination and lumbar puncture. Bloody spinal fluid is diagnostic but does not exclude the additional possibilities of subdural or intracerebral hemorrhage.

If blood is present in the spinal fluid, factor therapy should continue for at least one week to 10 days or resolution of the patients symptoms. Ambulation should be gradually resumed but the patient cautiously observed for recurrent bleeding. Recovery is usually uneventful. It must be kept in mind that hemorrhage or onset of symptoms may be delayed for days following the onset of trauma or hemorrhage.

3. Intracerebral hemorrhage. Intracerebral hemorrhage (ICH) is the most ominous occurrence in the hemophiliac (3, 36). Occurrence usually follows trauma with the onset of diminished level of consciousness, seizures and focal neurologic signs. Though usually abrupt, symptoms may begin gradually with headache and meningeal signs and then progress in hours to days to coma and demise. Treatment must be rapid and often agressive, including prompt replacement therapy, steroids, lumbar puncture and in cases of persistent progression, appropriate contrast studies. Computerized scanning should be utilized promptly and will in most instances provide a safe noninvasive approach negating the need for angiography or pneumoencephalography.

Surgery may infrequently be necessary when increased intracranial pressure cannot be controlled, or the patient's neurologic state does not stabilize despite appropriate replacement of factor material and prompt use of steroid therapy. With prompt recognition of threat or diagnosis of intracerebral bleeding most patients tend to stabilize and make at least a partial recovery. However, most deaths with hemophilia occur as a result of ICH, often in spite of the most vigorous and agressive therapy. In those patients with recovery, morbidity is high with residual hemiparesis, sensory and visual disorder, diminished mental function and often with seizure disorder. Physical and rehabilitation therapy and antiseizure medications should be employed as with any other cerebral vascular episode.

Conclusion

The nervous system is distinctly at risk in hemophiliacs. There is an approximate 25% risk factor slightly greater for central injury as compared to peripheral nervous system involvement (14.9% and 12.9% respectively). The distribution of complications in the present series of 201 patients is not greatly different from those prior to the advent of more modern therapy. The most common syndromes include subarachnoid hemorrhage (43.1%), intracerebral hamorrhage (27.5%) and femoral neuropathy complicating iliac muscle hemorrhage (31.4%).

All three deaths in this series occurred with intracerebral hemorrhage, demonstrating that it is the most serious complication to which hemophiliacs are subject.

Prompt recognition and rapid treatment reduce morbidity and promote more normal life for the affected hemophilic patients.

References

1. Bulloch, W. and Fildes, P.: *Treasury of Human Inheritance.* Dulau and Co., London 1912.
2. Seddons, H. J.: Hemophilia as a Cause of Lesion in the Nervous System, Brain 53:306–310, 1930.
3. Chalgren, W. S.: Neurologic Complications of the Hemorrhagic Diseases, Neurol, 3:126–136, 1953.
4. Douglas, A. S. and McAlpine, S. G.: Neurologic Complications of Hemophilia and Christmas Disease, Scot Med J 1:270–273, 1956.
5. Silverstein, A.: Intracranial bleeding in Hemophilia, Arch Neurol 3:141–157, 1960.

6. Silverstein, A.: Intracranial Hemorrhage in Patients with Bleeding Tendencies, Neurol 11:310–317, 1961.
7. Silverstein, A.: Neuropathy in Hemophilia, JAMA 190:554–555, 1964.
8. Kerr, C. B.: Intracranial Hemorrhage in Hamophilia, J. Neurol Neurosurg Psychiat 27:166–173, 1964.
9. Potter, J. M.: Head Injury and Hemophilia, Acta Neurochir 13:380–387, 1965.
10. Fessey, B. M. and Meyness, M. J.: Haemorrhage Involving the Central Nervous System in Haemophilia: Account of the Management of Five Cases, Brit Med J 2:211–212, 1966.
11. Goodfellow, J., Fearn, C. B. d'A. and Matthews, J. M.: Iliacus Hematoma. A Commmon Complication of Haemophilia, J Bone Joint Surg 49:748–756, 1967.
12. Duthie, R. B., Matthews, J. M., Rizza, C. R., Steel, W. M. and Woods, C. G.: The Management of Musculo-Skeletal Problems in the Haemophilias. Bleeding into Muscles and Its Consequences; Neurological Involvement. Blackwell Scientific Publ., Oxford, London, 1972, ch. 5, p. 56.
13. Ibid; Perhiperal Nerve Lesions, Ch. 5, p. 63, 1972.
14. Seeler, R. A. and Imana, R. B.: Intracranial Hemorrhage in Patients With Hemophilia, J Neurosurg 39:181–185, 1973.
15. Wintrobe, M. M., et al.: The Hereditary Coagulation Disorders - Hemophilia A and Hemophilia B. In *Clinical Hematology*. Lea and Febiger, Phila., Part IV, Sec. 3, Ch. 37, p. 1161–1173, 1974.
16. Pool, J. G. and Robinson, J.: Observations on Plasma Banking and Transfusion Procedures for Haemophiliac Patients Using a Quantitative Assay for Antihemophilic Globulin (AHG), Brit J Haematol 5:24, 1959.
17. Pool, J. G. and Shannon, A. E.: Production of High-Potency Concentrates of Antihemophilic Globulin in a Closed-Bag System, New Engl J Med 273:1443, 1965.
18. Bidwell, E., Booth, J. M., Dike, G. W. R., and Denson, K. W. E.: The preparation for Therapeutic Use of a Concentrate of Factor IX Containing Also Factors II, VII and X, Brit J Haematol 13:568, 1967.
19. Brinkhous, K. M., Shanbrom, E., Roberts, M. R., Webster, W. P., Fekete, L., and Wagner, R. M.: A New High Potency Glycine-Precipitated Antihemophilic Factor (AHF) Concentrate. Treatment of Classical Hemophila and Hemophilia with Inhibitors, JAMA 250:613, 1968.
20. Biggs, R., Eveling, J. and Richards, G.: The Assay of Anti-Hemphiliac Globulin Activity, Br J Haematol 1:20–34, 1955.
21. Biggs, R.: Clinical Experience With Factor IX Concentrate of Bidwell. *Hemophilia and the New Hemorrhagic States. International Symposium, New York*. Ed. K. M. Brinkhous. The Univ N Carolina Press Chapel Hill 1970, p 31.
22. Green D: Therapeutic Materials. In *Hemophilia*. Edited by D. Green and C. Thomas. Springfield, Ill. 1973, Ch. 2, p. 18–20.
23. Britten, A. F. M.: Hemophilia - Where Are We Now ? In *Hemophilia. Proceedings of the VII Congress of the World Federation of Haemophilia*, 1971. Edited by F. Ala and K. W. E. Denson, Excerpta Medica, Tehran, 1973, p. 247–248.
24. Gendelman, S., Aledort, L. and Hollin, S.: Intracranial Meningioma in Factor IX Deficiency. *Proceedings of the X Congress of the World Federation of Hemophilia*. Helsinki, Finland, 1975.
25. Biggs, R. and MacFarlane, R. G. (eds): *Treatment of Hemophilia and Other Coagulation Disorders*. Blackwell, Oxford, London 1966.
26. Blattner, R. J.: Recent Developments in the Management of Hemophilia with Particular Reference to Intracranial Bleeding, J Pediat 70:449, 1967.
27. Nilsson, I. M.: *Hemorrhagic and Thrombotic Diseases*. J. Wiley and Sons, New York, 1974.
28. Olsen, E. R.: Intracranial Surgery in Hemophiliacs: Report of a Case and Review of the Literature, Arch Neurol 21:401–412, 1969.
29. Rudowski, W. J. and Ziemski, J. M.: Extensive Surgical Procedures in Patients with Hemophilia A, Surg Gynecol Obstet 135:571–576, 1972.
30. Ratinoff, O. D.: The Future Research and Therapy, in *Hemophilia*. Edited by D. Green and C. Thomas., Springfield, Ill., 1973, Ch. 10, pp. 101–111.

31. Fearn, C. B. d'A: Iliacus Haematoma Syndrome as a Complication of Anticoagulant Therapy, Brit Med J 4:97–98, 1968.
32. Weintraub, M. I.: Acute Femoral Neuropathy Secondary to Consumption Coagulopathy, NY State J Med 71:2670–2671, 1971.
33. Kerr. C. B.: Intracranial Hemorrhage in Hemophilia, J Neurol Neurosurg Psychiat 27:166–173, 1964.
34. Tarnay, T. J.: Surgery in the Hemophiliac, Charles C Thomas. Springfield, Ill 1968, P.89–105.
35. Quick, A. J.: *The Hemorrhagic Diseases and the Pathology of Hemostasis.* Charles C Thomas, Springfield, Ill. 1974, p. 285–286.
36. Seeler, R. A. and Imana, R. B.: Intracranial Hemorrhage in Patients with Hemophilia, J Neurosurg 39:181–185, 1973.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May–June, 1977
Printed in U.S.A.

Dental Treatment for Hemophiliacs: Evaluation of Dental Program (1975–1976) at The Mount Sinai Hospital International Hemophilia Training Center

BRUCE E. EVANS, D.M.D

Introduction

Dental disease may be the most common health problem in the world; the prevalence of dental caries in the United States approaches 100 percent (1). Unfortunately many hemophiliacs have never had adequate dental care (2). As a consequence, dental complications have often been a cause of hospitalization for these patients. Hemophiliacs have had to face periods of treatment of two weeks or longer to correct dental problems. Such treatment involves significant drain on blood products, finances, and health professional manpower; and has caused severe interruptions in the scholastic or work schedules of these patients (3).

Because of recent advances in component therapy, the clinical treatment of hemophilia has been greatly modified. Self-infusion and home therapy programs have been developed (4–8). What might formerly have been considered a crisis for a hemophiliac can now be readily included in the patient's routine maintenance. The dentist treating hemophiliacs is able to shift his focus from situations involving dental emergencies and extractions to comprehensive dental treatment for the hemophiliac.

However, despite an improved understanding of blood coagulation and major advances in the management of the bleeding disorders, hemophilia patients still do not receive optimal dental treatment. Recent literature has indicated significant progress in oral surgery treatment for these patients. (3, 4, 9–12). Unfortunately, the primary focus of these reports has been dental extractions rather than conservation of the dentition and promotion of oral health. Admittedly, many hemophilic patients do require oral surgery to correct long-standing dental neglect. However, the dental profession must be made aware of the possibilities of general dental treatment for hemophiliacs. Current modes of therapy enable us to manage bleeding crises successfully. Considering routine general dental treatment, bleeding situations are uncommon. Consequently, quality comprehensive dental treatment should be available for hemophilia patients and a commitment should be made to provide such treatment.

Hemophiliacs should expect good oral health. Any dentist with a basic understanding of normal hemostasis, as well as of the nature of the hemophi-

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From the Department of Dentistry and Oral Surgery Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Bruce E. Evans, D.M.D., 630 Fifth Avenue, Suite 1856, New York, N. Y. 10020.

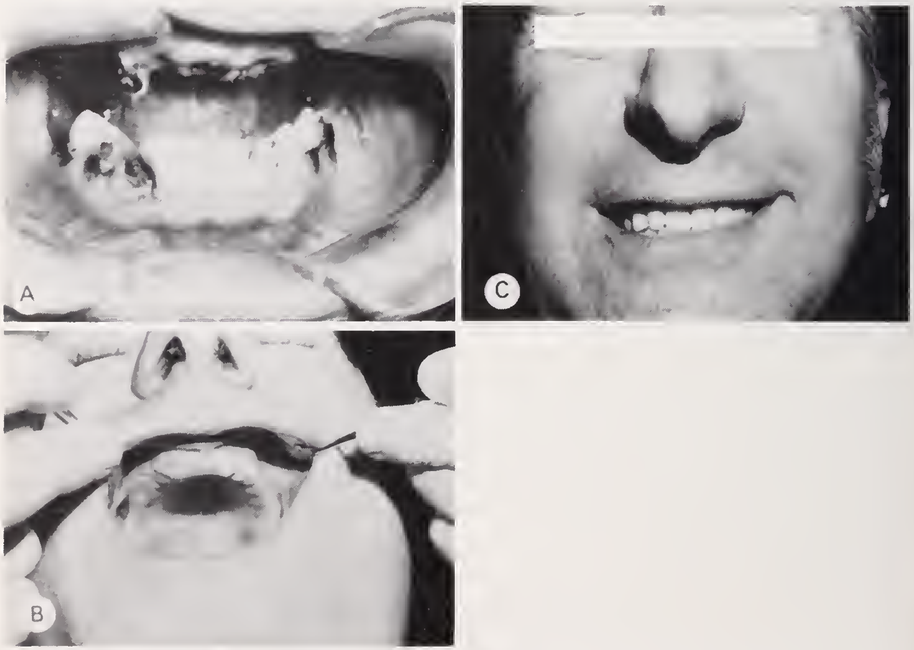
lioid disorders, can safely and effectively treat the hemophilic patient. Except for certain modifications in dental techniques, routine dental care for the hemophiliac is the same as for a nonhemophiliac.

This article comprises two sections regarding dental treatment for hemophiliacs. Part I presents a general comprehensive review of dental treatment for hemophilic patients and consists of a multitude of recommendations derived from experiences in the dental treatment program of the International Training Center for Hemophilia of the Mount Sinai Medical Center. Part II is an evaluation of that program during the recent clinical year of 1975–1976.

SECTION I

Dental Treatment for the Hemophiliac

The hemophilic disorders do not directly cause dental problems. Hemophiliacs are susceptible to dental disease just as normal patients are. Previously the high incidence of dental problems among hemophilic patients was due to neglect or lack of dental care and was secondary to the bleeding disorder (Fig. 1a). Fear of bleeding during dental treatment, both on the part of patients and dentists, has been the primary reason for lack of good dental treatment for hemophilic patients.



FIGS. 1a. Preoperative condition of a 45-year-old moderate hemophiliac (Factor VIII 8.7%). This patient suffered from long-standing dental neglect. 1b. The same patient 8 weeks postoperatively following the removal of his remaining dentition. 1c. The same patient following restoration of normal esthetics and function with full denture prostheses.

To provide effective dental treatment for hemophilic patients it is necessary:

1. To educate patients and their physicians regarding the existence and recognition of dental disease.
2. To educate dentists regarding hemophilia and the methods of treatment currently available for hemophilia.
3. And finally to *deliver* care to the patients.

We now realize that there are no general dental procedures which cause significant bleeding in hemophilic patients; consequently, there should be no compromise in the quality of dental care for hemophiliacs. (Surgical and periodontal procedures will usually result in bleeding, but there are effective methods to prevent or to control such bleeding if it occurs). Regular comprehensive dental care, including semi-annual examinations, proper oral hygiene, and patient/parent education, minimizes the need for extractions and extensive dental restorations.

The recent changes in the treatment of hemophilia appear to have separated the population of hemophiliacs into two types of dental patients. The first group is predominantly younger—children and adolescents who have enjoyed the recently available benefits of factor concentrates, and who have been able to obtain good dental treatment without fear of bleeding. It is especially important to initiate these patients into the basic principles of good oral health and to guide them in maintaining healthy mouths and in continuing good dental treatment.

Older hemophiliacs require correction of existing dental problems followed by restoration of good dental health. This second group of patients, primarily adults, did not have available the factor concentrates to protect them from bleeding episodes. As a consequence, these patients rarely received good dental treatment. Our approach for these patients is dental rehabilitation (unfortunately, often with many extractions), replacing missing teeth with bridges, partial dentures, and full dentures where necessary. (Figs. 1b and 1c.)

The general dentist/private practitioner is capable of doing dental exams for hemophiliacs in his own office. If the dentist is aware of the disease and if he will exert minimal precautions (particularly with local anesthesia), he should be able to provide routine dental care without complications. Any questions should be directed to the patient's hematologist or to the physician primarily responsible for the care of the patient's hemophilia. Any dental treatment which is not routine and which might involve bleeding should be handled by a dentist or oral surgeon familiar with the management of hemophilic patients. Should an uncommon bleeding crisis arise during dental treatment, there is safe and effective treatment available to manage the hemophiliac.

Patient Evaluation

As with any patient, prior to providing dental treatment a complete medical-dental history should be obtained and an oral examination performed.

Pertinent hemophilic history should include the type and severity of the patient's disorder, presence of inhibitor, family history, medications used for pain, and whether or not the patient is on home therapy. Previous dental experiences and treatment should also be documented. It is important to discuss this information and the anticipated treatment plan with the hematologist or the responsible physician.

Dental radiographs are necessary for complete diagnosis; for the hemophiliac it is necessary to exercise caution in the placement of periapical films to avoid traumatizing tissues and producing sublingual hematomas. If dental impressions are required for evaluation, the dentist should exert care in the placement of impression trays. The borders of the trays should be edged with periphery wax to minimize trauma to the soft tissue.

Many hemophilic patients receive frequent plasma product factor replacement therapy to control bleeding. The source of these blood products may consist of thousands of donors and many *hemophiliacs* have had hepatitis. Thus all instruments used with hemophilic patients must be sterilized by autoclave as a precaution against the transmission of hepatitis.

Prevention of Dental Disease

Inadequate dental treatment only encourages eventual complications for all patients. Obviously it is in the best interest of the hemophiliac to limit his dental problems. The dentist who treats a hemophiliac must make a great effort to explain the principles of preventive dentistry to his patient (13).

Oral hygiene. Prevention is best initiated by the patient in his home environment. Maintaining oral hygiene is not the total solution to dental disease; but it may prevent, or certainly aid in the control of dental decay and periodontal disease. The concept of good home care must be emphasized, particularly to those disabled patients for whom frequent visits to the dental office are imporssible.

The hemophiliac should understand the principals of *toothbrushing* which will remove plaque and clean the teeth (Fig. 2). He must learn to massage, but not abrade the gingiva. The dentist must dispel the fear of gingival bleeding; *good oral hygiene will reduce and eventually eliminate this bleeding from the gingival tissues.* The hemophilic patient should use a soft multitufted toothbrush of an appropriate size. Brushing techniques should be adapted to age, dexterity, and dentition, and are the same as those for normal patients. Disclosing agents available from the pharmacy are useful to demonstrate tooth cleanliness and to identify the dental plaque.

Hemophiliacs should be instructed to carefully pass dental floss through the contact points between teeth to remove all debris and plaque. When flossing is correctly performed, interproximal hemorrhage does not occur. Slight gingival bleeding caused by flossing is not a reason for concern. Water irrigating devices used in conjunction with toothbrushing and flossing can also be effective in oral hygiene at home.

Fluoride. The long-range benefits of fluoride are important to the child and may be particularly beneficial to the hemophiliac. Water fluoridation result-

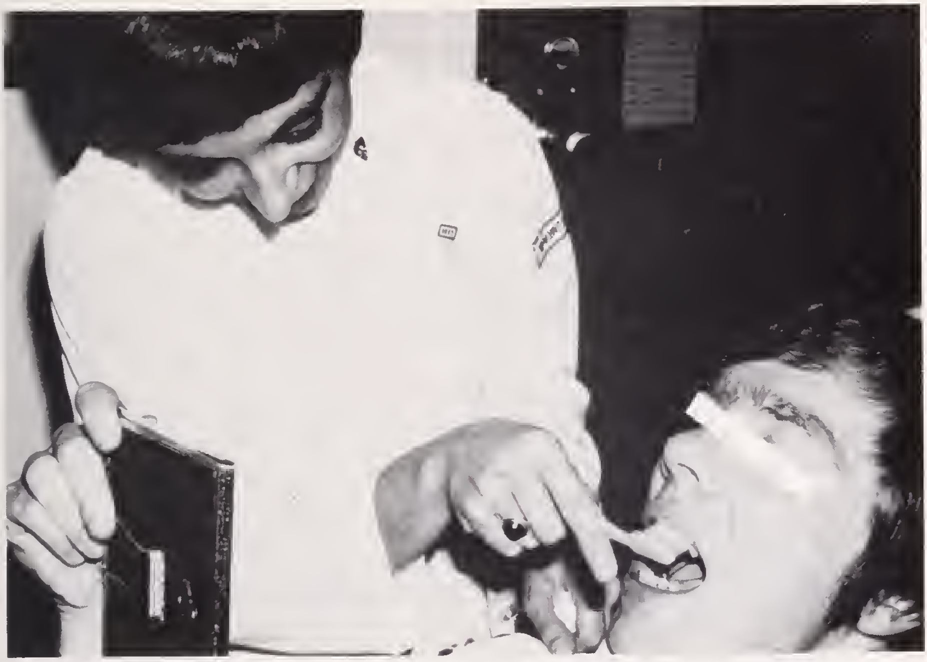


FIG. 2. A 30-year-old severe hemophiliac (Factor VIII less than 1%) enrolled in a dental home care program learning brushing technique from the dental hygienist.

ing in systemic administration of one part fluoride per one million parts water is recognized as an ideal public health measure for effective reduction of tooth decay. If the regular community water supply is not fluoridated, daily fluoride supplements in the form of drops, tablets and, fluoridated bottled water are recommended for children from birth through twelve years of age. In caries-susceptible patients, topical fluoride gel can be used at home as often as required and can be continued throughout the adult years.

Nutrition – Diet. Selection of an adequate and balanced diet is imperative. Some hemophilic patients choose soft foods in an effort to avoid gingival bleeding. On the contrary, patients should be taught to avoid caries-producing foods which are soft, sweet, starchy, and gummy. They must be encouraged to select a diet beneficial to their oral and general health.

Visits to the dentist – Check-up. Hemophilic patients should have routine preventive dental treatment in the office on a regular basis. The best time for a child's first visit to the dentist is between 12-18 months of age; hemophilic children are no exception. Most patients should be on a six-month recall program; patients with a high DMF (Decayed, Missing, Filled) index and poor hygiene should be more closely supervised and should be evaluated more frequently. At each recall visit the teeth are scaled and polished, treated with fluoride, and x-rayed as indicated.

Calculus present in the mouth of a hemophiliac should be removed without trauma to the gingival tissue. Superficial bleeding resulting from careful scaling ceases within a reasonable time, as will the slight hemorrhages which may occur with prophy-cup polishing. Patients who require deep scaling because of gross calculus should be initially scaled supragingivally. The tissue should be allowed to heal for 7–14 days during which time the gingiva recedes as edema and hyperemia diminish. Subsequent treatments to remove calculus and irritants will incur less risk of bleeding from the tissue.

If replacement therapy of Factor VIII or IX is utilized for scaling procedures, the entire mouth should be scaled in a single session if possible. This reduces the increased risks inherent in multiple transfusions and eliminates the additional expense of blood products for subsequent appointments. Sufficient time should be allowed so that procedures may be performed with extra caution. For subgingival scaling, hand instrumentation with proper finger rests is recommended for the removal of calculus with minimal trauma. Packing the sulcus with retraction cord can be helpful in obtaining access to remove gross calculus. If the cavitron is used for removal of gross supragingival calculus, it must be used with caution.

> **It is hoped that the patient who has been made aware of the importance of dental hygiene will become interested in his mouth and teeth and will strive to prevent decay, periodontal disease, and other oral health problems.**

Pain Control

Anesthesia and analgesia. The management of pain for the hemophilic patient has always presented a challenge to the physician and dentist. Prior to the development of replacement therapy, local anesthetics were rarely utilized for dental procedures. Today, the judicious use of concentrates to manage the patient's hematologic disorder, enables us to offer any analgesic or anesthetic modality required to provide the necessary dental treatment for a hemophiliac. This approach for local anesthetic techniques differs from previous recommendations in the literature (14).

No patient should be expected to suffer painful procedures. Treatment without the elimination of pain increases the patient's apprehensions, usually leads to a decrease in cooperation, and inevitably results in inferior dental care.

Local anesthesia. Certain children do better with local anesthesia than without it; others have become so fearful of needles that anesthetic injections are a source of psychological trauma. It may be possible to perform restorative dental procedures on primary teeth and on some permanent teeth without local anesthesia. Success for such procedures without anesthesia will depend on a gentle touch and very sharp burs under minimal pressure at high speeds.

Intrapulpal injections can usually be administered without much concern for bleeding and rarely require coverage with factor replacement. Particularly for extractions, peridental injections with a short 30-gauge needle may be administered into the periodontal membrane space on the four axial surfaces of the tooth.

All block anesthetics and some infiltration anesthetics require prior replacement therapy, so that the plasma factor is elevated to the accepted surgical hemostatic level of 30% at the time of administration of the anesthetic (15).

The morbidity caused by hematoma formation after injection of local anesthesia is dependent on the anatomy of the injection site. When an infiltration injection is administered in an area where the tissue is firm and confined the chance of a bleeding complication is less likely (Fig. 3). However, *the loose connective, nonfibrous, and highly vascularized tissue where the mandibular blocks and the posterior superior blocks are administered is predisposed to the development of a dissecting hematoma* which has the potential of obstructing the airway and of creating a life-threatening crisis (Fig. 4).

Block anesthetics must be given with extreme caution; it is possible to safely administer such anesthetics only with adequate preoperative replacement therapy. If such injections produce no bloody aspirate and there is no hematoma formed subsequently, further replacement therapy is usually not necessary. However, the patient must be observed for the possible development of hematoma. There is a greater chance of hematoma formation if a bloody aspirate was observed at the time of injection. Should a hematoma develop, ice applied to the area will limit its spread; but ice is not a substitute for rapid and adequate replacement therapy. The hematologist should be notified immediately to manage further infusion of the necessary factor.

Patients receiving local anesthetics must be warned of subsequent numbness of the soft tissues. The lack of sensation will last for an hour or more; and children particularly should be observed so they will not purposely or inadvertently bite the lip, tongue, or cheeks. (Local anesthesia without a vasoconstrictor will shorten the duration of the anesthetic and may eliminate postoperative lip-chewing in children).

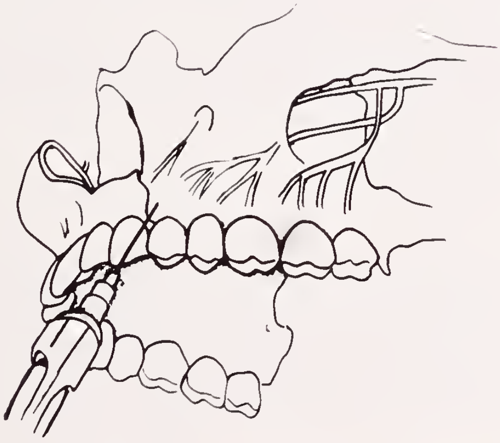


FIG. 3. Infiltration local anesthesia may be administered without prior replacement therapy in an area where the tissue is firm and confined without the development of hematoma or other bleeding complication.

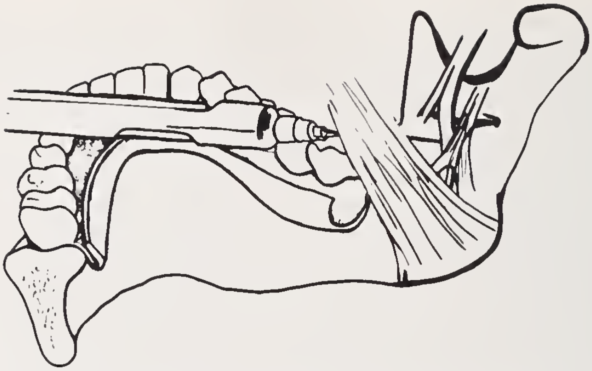


FIG. 4. Loose connective, nonfibrous, and highly vascularized tissue in the area where the mandibular block is administered is predisposed to the development of a dissecting hematoma and such a block should not be administered unless the patient has received replacement therapy.

Preoperative sedation. Premedication with hypnotic, analgesic, or tranquilizing agents may be an aid to management, and is especially useful for long surgical and operative procedures. Premedication may be indicated for problem children and for fearful, nervous and apprehensive adults. This technique can prove a worthwhile adjunct where raising the pain threshold or relaxing the patient is indicated. Medications may be administered orally, by suppository or by the intravenous route. *Intramuscular injections are contraindicated for the hemophiliac because of formation of hematomas* (16).

Inhalation analgesics. Many patients claim they are fearful and apprehensive that a dental procedure will hurt, although they acknowledge that they are not actually having pain. Nitrous oxide inhalation analgesia can be used as an adjunct to allay mild pain sensation and apprehension without loss of consciousness.

General anesthesia. General anesthesia is the most effective technique to manage patients who are uncooperative or who must undergo extensive restorative treatment and/or complicated painful procedures. The intravenous route is safe for the hemophiliac; the intravenous technique itself does not cause bleeding problems and does not require infusion replacement of the deficient Factor VIII or IX. The intravenous route may be used to sustain an ultralight level of general anesthesia utilizing a short-acting barbiturate. (Fig. 5)

When *inhalation* general anesthesia is administered, endotracheal intubation is sometimes indicated. Because of the possible trauma associated with intubation, prophylactic factor replacement is mandatory for any hemophiliac who requires an intubation. Oral intubations result in less trauma to tissues than do nasal intubations; therefore this technique is preferred for the hemophilic patient. However, we strongly advise against intubating hemophilic patients.

Hypnosis. This modality has been reported to be effective in the management of fear and anxiety. The effectiveness of hypnosis has been demonstrated in the control of emotionally induced bleeding and in the management

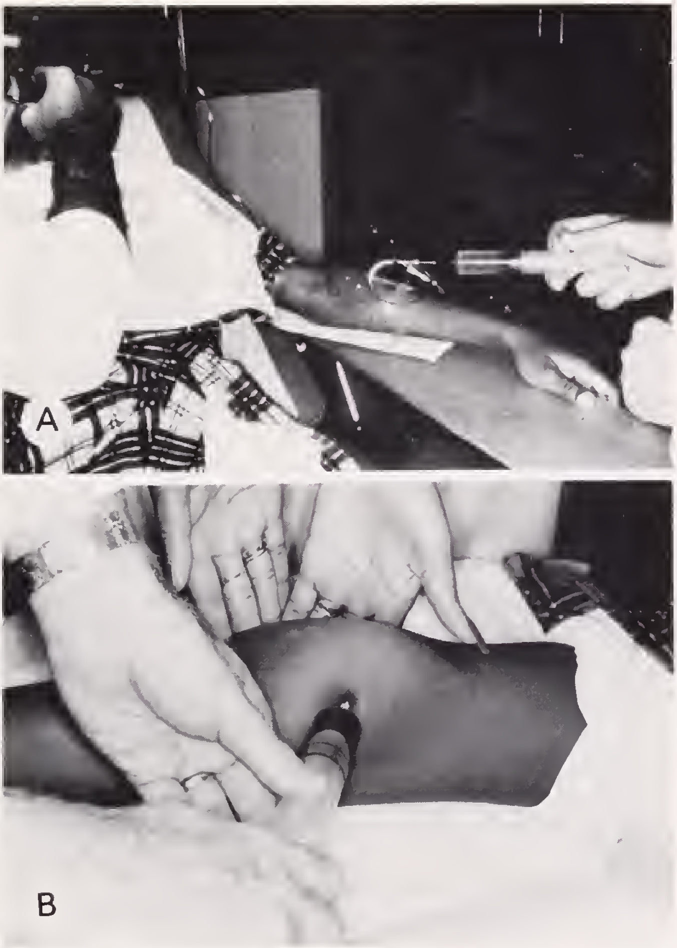


FIG. 5. Intravenous anesthesia for a 14-year-old Factor VIII 1% hemophiliac undergoing extraction of a tooth, simultaneously with aspiration of a hematoma of the knee of Team members in The International Training Center for Hemophilia at The Mount Sinai Hospital in New York.

of the hemophiliac undergoing tooth extraction. Further study of this method is needed (17, 18).

Analgesics. The dentist must be cautious in prescribing analgesic medications for hemophilic patients because of problems caused by certain agents. Hemophiliacs experience pain when they bleed spontaneously into soft tissues and joints, and from the chronic persistent pain of arthritis and permanent joint changes. Additionally, hemophiliacs may have developed a low tolerance to pain. It is not unusual for a hemophiliac to require more potent analgesics than normal patients.

Analgesics containing aspirin, and classical antiinflammatory agents (such as Butazolidine and Indocin) are contraindicated at all times because they potentiate the bleeding disorder by altering platelet function. For dental pain it is important to omit all analgesics (such as the compound drugs Percodan or Empirin) that contain aspirin (16).

Those analgesics which can safely control pain for the hemophiliac are:

Nonnarcotics—Tylenol, Talwin, Darvon (plain)
Narcotics—Codeine, Demerol, Morphine, Dilaudid (All habit-forming, all have some side effects)

General Dental Treatment

Restorative procedures. Restorative procedures performed for the nonhemophiliac can usually be performed in a similar manner for the hemophiliac. (9). Although it may be necessary to exert added caution to provide safe dental treatment, quality dental care is never compromised. Preparation of the tooth is not modified because the child or adult has hemophilia. The usual principles of good restorative dentistry are observed.

A rubber dam with Young's frame should be used to isolate the operating field. Thin rubber dam is preferred because there is less tendency to torque the rubber dam clamp, thereby avoiding abrasion of gingival tissues. Selection of clamps should be made to reduce tissue trauma. The clamp should be carefully placed; it should be stable so it does not slip and lacerate the gingival papilla. The rubber dam not only isolates the area, but also retracts the cheeks, lips and tongue. Since these areas are highly vascular, their accidental laceration by the high speed drill could present a difficult and dangerous management problem.

Wedges and matrices can be used conventionally. A wedge is always placed interproximally during proximal preparations. The wedge retracts the papilla, thus protecting it and minimizing trauma. Matrices, when carefully placed, will cause no bleeding problems.

High speed vacuum and saliva ejectors must be used with caution so that sublingual hematomas are not created. Those ejectors with rubber padded tips are preferable since sublingual tissue cannot be drawn into the opening.

Amalgam and synthetic restorations are rountinely prepared for the hemophilic patient. The preparation of the tooth for a cast crown presents no problems if care is used in gingival preparation. Packing of the gingival sulcus with hemostatic retraction cord is advantageous when there is extensive subgingival decay. Care is used in placement of retraction cord and in taking impressions. As previously mentioned, periphery wax is used on the tray to prevent possible intraoral laceration during tray placement. No undue trauma should be created in cementing or finishing the crown.

There are certain procedures unique to the child patient (19–21). The preparation for a stainless steel crown should be done in the routine manner for the hemophiliac as for the normal patient, with the crown adapted to fit about 1 mm below the gingival tissue.

Treatment of deep caries—Pulpal therapy. There is no contraindication for performing endodontic therapy for hemophilia patients (9, 22). Pulpal therapy or root canal therapy can enable a patient to retain and maintain badly needed teeth. Some patients come to the office for the first time with rampant deep caries. Pulp exposures in primary and permanent teeth may sometimes be avoided in such teeth if the carious dentin is not entirely removed in one procedure. Pulpotomy, pulpectomy, and root canal filling are all preferable to extraction. The replacement of a missing tooth is an expensive procedure; for a hemophiliac the extraction of a tooth and its subsequent replacement implies complicated treatment.

Anesthetics are usually unnecessary when the pulp is necrotic. If the nerve tissue of a vital tooth is exposed, the intrapulpal injection may provide sufficient anesthesia; or the patient may be medicated or receive general anesthesia. Usually any bleeding from endodontic procedures is insignificant and does not require factor infusion. Hemorrhage produced during pulp amputation or vital extirpation is controlled by pressure and/or a hemostatic agent such as epinephrine on a cotton pellet. Bleeding that is difficult to control usually indicates inadequate removal of tissue remnants in the canal. If necessary, to control hemorrhage, cotton is soaked in formocresol and dried, and then sealed into the pulp chamber for a week to mummify and fix the pulp tissue. The control of bleeding in pulpal therapy has not presented any problems in our experience with hemophiliacs.

When root canal therapy is performed for hemophiliacs, the dentist should be cautious to avoid instrumentation and filling beyond the apex of the root of the tooth. To prevent any periapical bleeding from occurring, it is recommended that canals be filled 1 mm short of the radiographic apex of the vital root, and to the radiographic apex of nonvital teeth (9).

Prosthetics. The hemophiliac should be allowed to entertain the prospect of whatever best suits his needs. He is capable of undergoing whatever preparation may be involved for the artificial replacement of teeth including crowns, bridges, partial dentures and full dentures.

The execution of fixed prosthetic work is straightforward and employs techniques previously mentioned. Individual crowns with posts and cores, bridges, and splints should be used for the hemophiliac where indicated. Impression and other techniques involved in the fabrication of partial or complete dentures do not cause bleeding (9).

Except in the most extreme circumstances, all oral pathology should be cured to establish a healthy preprosthetic foundation which will in turn enhance the future oral condition. Many older hemophiliacs have multiple and complicated dental problems. These patients have bad memories of bleeding situations which occurred before factor concentrates were available. Adequate treatment for these patients may include the extraction of numerous chronically infected or otherwise nonrestorable teeth. Rehabilitation of the oral cavity by replacing these unhealthy teeth with partial or complete dentures will restore normal function and esthetics (Figs. 1a–c).

Periodontal treatment. Periodontal disease is significant as the major cause of tooth loss among adults and should be prevented or adequately managed. All hemophilic patients should undergo routine periodontal examination and evaluation including probing and measuring of pocket depth (Fig. 6).

Treatment of gingivitis for the hemophilic patient requires the initial correction of local factors, including calculus deposits, faulty restorations,

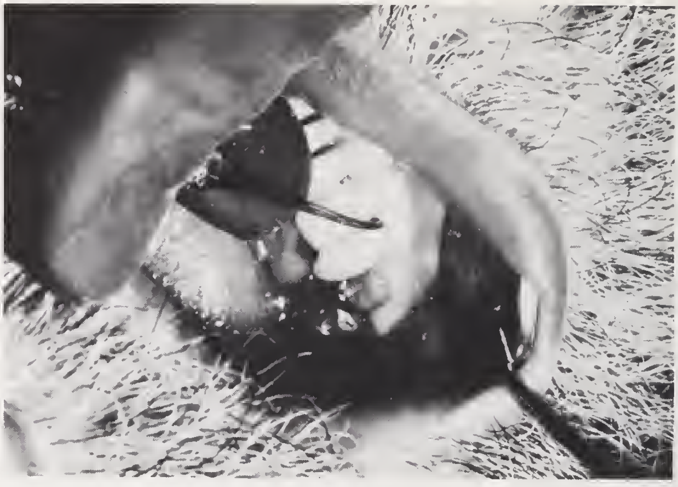


FIG. 6. 65-year-old Factor VIII 23% hemophiliac undergoing routine periodontal exam. This patient has a history of good dental treatment, including root canal therapy.

and traumatic occlusion, in an attempt to reverse a gingival infection which can progress to involvement of the alveolar bone.

Minor periodontal procedures may be performed for hemophiliacs with no risk of stimulating significant bleeding, although a certain amount of oozing will undoubtedly be encountered. Probing and supragingival scaling are rountinely performed. As mentioned previously, careful hand instrumentation with fine scalers and curettes is best for atraumatic subgingival scaling to minimize the risk of bleeding. Short frequent treatments are desirable; edematous gingival tissue will shrink, allowing the deeper calculus to become more visible. It is imperative that periodontal patients be placed on a maintenance schedule for proper management.

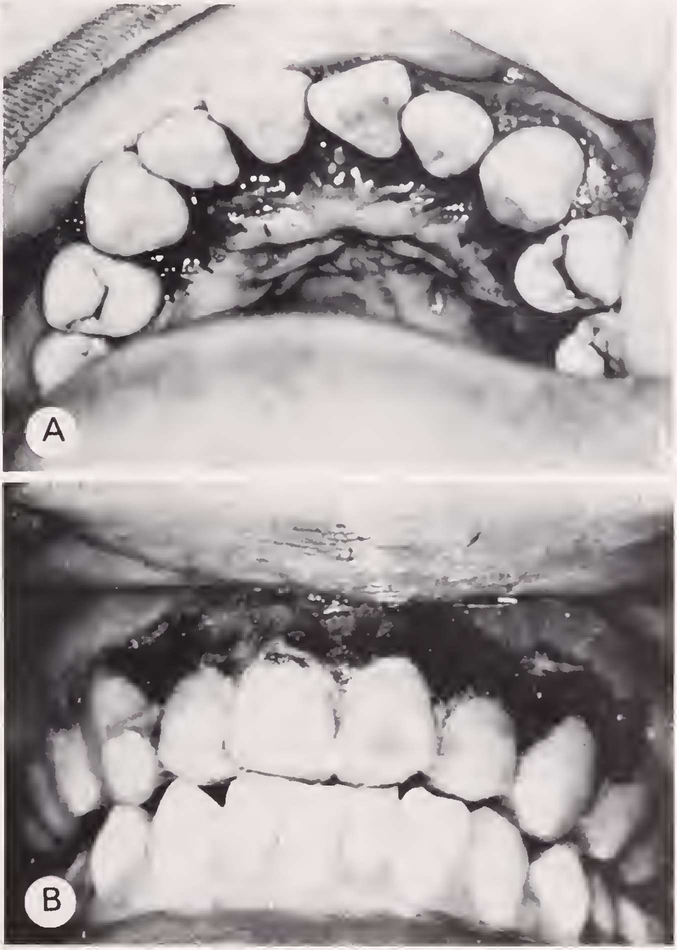
Gingival proliferation into deep carious lesions in the hemophiliac is usually treated by placement of a dressing of zinc oxideeugenol to obtain shrinkage of excess tissue. Electrosurgical procedures incur a risk of subsequent bleeding. Therefore, electrosurgery is *not* recommended for the hemophiliac, and the use of zinc oxide-eugenol dressing is the treatment of choice.

An abnormal frenum attachment may cause gingival recession and pocket formation. Early treatment is indicated to prevent continued recession of gingiva and loss of alveolar bone. Any appropriate frenectomy technique is surgically acceptable for the hemophiliac. However, frenectomy and other surgical periodontal procedures induce bleeding. Although periodontal surgery is indeed possible for the hemophiliac, sometimes it may be best managed in a hospital environment, with the requisite preparation. Any surgical procedure must always be coordinated with the hematologist for control of any anticipated bleeding (Figs. 7a and 7b).

Orthodontic treatment. There is no contraindication to orthodontic therapy for improving the oral health and appearance of the hemophilic child. With care, minor and major tooth movement may be accomplished without fear of stimulating bleeding. The decision to perform orthodontia for the hemophiliac is made using the same criteria as for any child (9).

Early recognition of an orthodontic problem is important for the hemophiliac because selective guidance can diminish or eliminate complex orthodontic problems. Both interceptive (preventive) and full-banded orthodontics are rountinely performed for hemophiliacs without bleeding complications. The choice of bicuspid or other extraction is determined individually. Indicated extractions are performed as elective surgery by the oral surgeon with the required preoperative evaluation and postoperative management (23) (See Oral Surgical Management).

Care must be taken in the adaptation and placement of bands to avoid the minor hazard of laceration of the oral muscosa, and to avoid protruding sharp edges and wires. Bleeding caused by an accidental scratch or minor laceration



FIGS. 7a. Periodontal surgery performed on a severe adult hemophiliac following factor replacement preoperatively. 7b. Use of a well-designed acrylic splint post operatively as a local measure (photographs: Drs. Matsuo and Uchida, Tokyo, Japan).

of the gingiva usually responds to pressure, with clotting taking place in 5 minutes. Preformed orthodontic bands and brackets which can be directly bonded to the teeth almost totally eliminate contact of orthodontic appliances with the gingiva during placement. Longer-acting wires and springs require less frequent adjustment of orthodontic appliances.

Oral hygiene is particularly important for the hemophilic patients undergoing orthodontic treatment to avoid gingival tissues becoming inflamed, endematous, and hemorrhagic from routine mastication. A water-irrigating device is an essential adjunct for good home care for the hemophilic child wearing orthodontic bands.

Oral Surgical Management

The climate surrounding surgical procedures for the hemophiliac has greatly changed since 1937 when Birch reported six deaths following tooth extraction, out of a total of 25 deaths due to exsanguination following surgical procedures. (24). Preoperative evaluation and postoperative management of the hemophilic patient undergoing an oral surgical procedure must be coordinated with the hematologist and the coagulation laboratory. The initial visit of the hemophilic patient is important to determine that all measures have been taken to avoid extraction. The dentist must explain the anticipated procedure to the patient and family to relieve their anxieties and to enlist their cooperation. In an *untreated* hemophiliac, postsurgical hemorrhage is inevitable. With adequate pre- and postoperative measures the hemophilic patient (without an inhibitor) can be safely managed so that *anticipated bleeding will be prevented.*

Today it is possible to perform oral surgery for the hemophiliac on an outpatient basis. Once the hematological management has been coordinated, the dentist may consider the feasibility of treating the patient as a hospital inpatient or outpatient or as an office outpatient (9, 11, 15, 23). Requirements are an experienced oral surgeon and hematologist, a facility available for the patient to receive pre- and postoperative infusions, and a coagulation laboratory capable of performing the necessary evaluations.

The oral surgeon should explain to the hematologist the surgical procedure, including the anesthetic technique, the degree of surgical trauma anticipated, and the duration of the recuperative period. Previous surgical experiences should be reviewed for each patient, and the current medical status should be assessed. The hematologist can then proceed to determine the amount of missing clotting factor required prior to surgery and can plan the postoperative management.

In computing the initial pre-surgical infusion we prefer to use sufficient replacement factor to raise the patient's deficient factor level to 60 or 70%. One hundred percent of a given factor is equal to one International Unit per cc of plasma. Plasma volume in an adult is 40 cc per kilogram of bodyweight. The average male weighs 70 kilograms and has an approximate plasma volume of 2800 cc. If his factor level were less than 1% he would require 2800 International Units to elevate his factor level to 100%. Fresh frozen plasma is assumed to include 1 unit of factor/cc and the requirement would be 2800 cc (an unworkable volume). If cryoprecipitate is administered, one assumes approximately 75–100 International Units of factor VIII per bag of cryoprecipitate; thus approximately 28 bags would be required for a patient who is less than 1% factor VIII. If concentrate is used, the specific number of International Units contained per bottle is clearly stated and can be assumed to be correct in most instances (8).

Where there is a question involving the patient's response to the administration of factor, it may be necessary to perform an infusion study prior to the actual surgical procedure. The coagulation laboratory should assess blood samples for factor levels prior to infusion, 15 minutes after infusion, and at appropriate intervals thereafter to determine the half-life of the administered product for a particular patient. The normal half-life for Factor VIII is anywhere from 6–12 hours and for Factor IX, 12–24 hours. With both substances there is an initial rapid disappearance followed by a slower rate of disappearance. The patient with a factor IX deficiency will have longer effect from the presurgical infusion than the patient with a Factor VIII deficiency. The severely afflicted patient (less than 1%) usually has a greater potential for postsurgical bleeding than the patient who has a mild form of the disease. However, individual patients manifest different responses to treatment and each case must be carefully prepared and observed.

At the present time, between 5–20% of hemophilia patients have antibody inhibitors capable of destroying the administered factor. It is essential that screening for this inhibitor be carried out prior to surgical intervention. If a hemophilic patient has an inhibitor, the administration of factor replacement therapy is contraindicated; extreme caution must be exercised in consideration of oral surgery. Close cooperation with the hematologist is imperative in management of such cases. Surgery for these patients, whether elective or emergency, must be limited and is not usually recommended. Should oral surgical treatment be necessary, local measures and adjunctive medications are utilized to control postextraction hemorrhage.

Adjunctive therapy. Since surgical patients undergo preoperative replacement of clotting factor, a clot will form following extraction of the tooth just as with normal patients. It is the preservation of this initial clot which is vital.

The clot may be protected by administering medication to inhibit the body's normal lysing process involving plasminogen which functions to break down the clot. Epsilon amino caproic acid (Amicar®, Lederle Laboratories, Pearl River, New York) has been very effective in the prevention of postextraction bleeding without the necessity of repeated infusions of the missing clotting factor. Amicar must be used on a strict schedule and for a period of time sufficient to allow primary healing to occur (3, 9–12, 23) (Figs. 8a and 8b).

Following the preoperative build-up of Factor VIII or IX and the subsequent oral procedure an initial dose of 6 grams of EACA is administered to adults as soon as possible. We are currently utilizing a regimen of 6 grams EACA every six hours for a period of ten days; EACA is available for oral administration in tablet or liquid. The drug is effectively absorbed by this

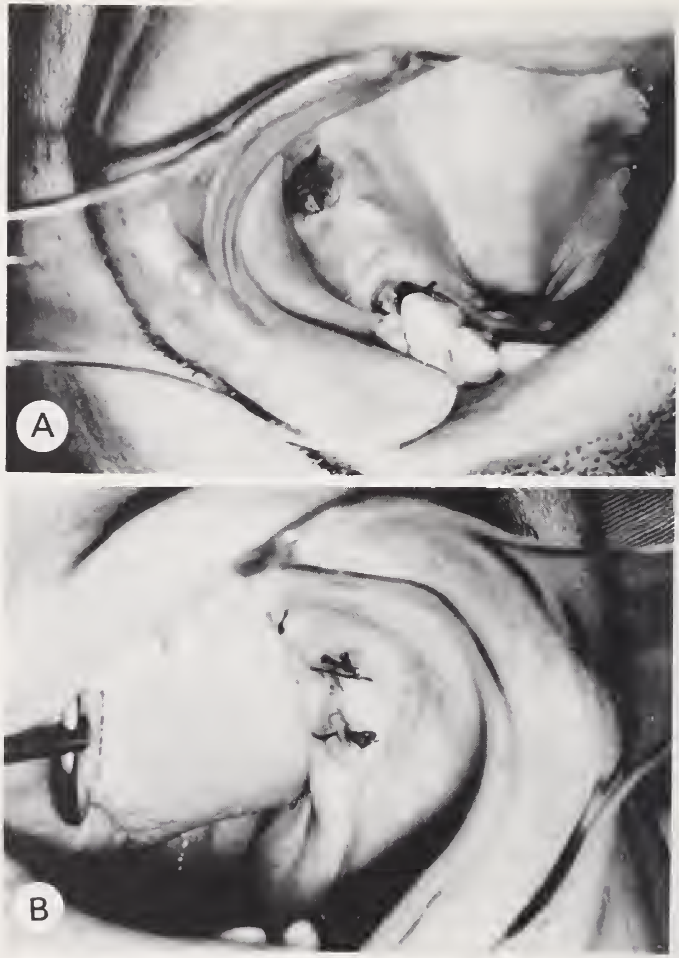


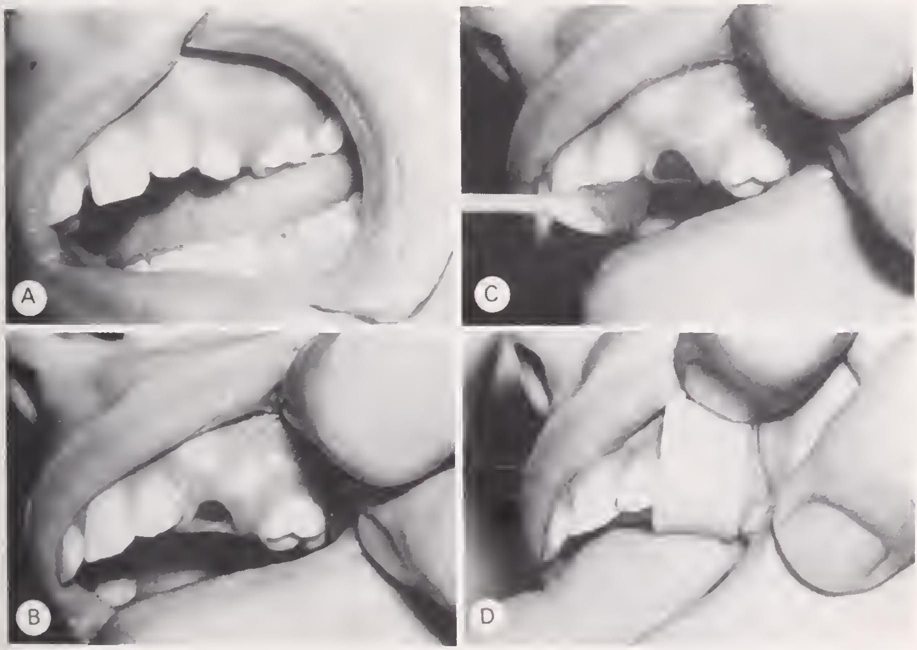
Fig. 8 a, b. Routine healing following mandibular and maxillary dental extractions at one week in a 45-year-old 4 ½ Factor VIII patient treated with EACA. This patient was treated with preoperative replacement therapy and local measures, and was maintained for 10 days on the Amicar regimen described.

route and rapidly cleared by the kidney. Renal bleeding or abnormal kidney function contraindicate the use of EACA. Our usual dosage of EACA for children is 100 mg/Kg body weight administered every 6 hours for a period of a week. Amicar liquid is recommended for children.

Extraction of deciduous teeth. A very common complaint of parents of hemophiliacs involves loose deciduous teeth which frequently cause bleeding in the mouths of hemophilic children. The sharp edges of the resorbing roots traumatize the gingival tissues and cause prolonged oozing. Primary teeth are not routinely removed prior to natural exfoliation. By the time deciduous teeth are sufficiently mobile to cause bleeding, they are no longer completely supported by bone. Radiographs usually indicate that the underlying permanent tooth is in the process of erupting. In cases where a loose deciduous tooth is tissue-borne, it may be possible to remove the tooth without administering any replacement therapy; bleeding in such situations is usually minimal and insignificant. A topical hemostatic agent such as thrombin or Microfibrillar Collagen Hemostat (Avitene®-Alcon, Avicon Inc., Fort Worth, Texas) can be applied directly to the wound to encourage clotting (25, 26). The extraction site may be protected for 12–36 hours by a cellulose bandage (Stomahesive®, E.R. Squibb & Sons, New York) (19). (Figs. 9a–d)

For more complicated removal of deciduous teeth, appropriate plasma products should be administered prior to extraction. At the discretion of the hematologist, replacement therapy may continue after extraction, or Amicar may be utilized. Contrary to previous opinion, there is minimal bleeding encountered following the removal of deciduous teeth and the elimination of the traumatizing sharp roots.

Extraction of permanent teeth. The surgical technique used to extract teeth of adult patients with hemophilia is the same as that used with normally clotting patients. The extraction should be as atraumatic as possible to the soft tissue and alveolar bone. Where there is a fracture of the alveolus, the loose bone fragments must be removed and the margins smoothed. The major differences in care for the hemophiliac as opposed to normal patients are the preoperative infusion of the missing factor and the postextraction treatment.



Figs. 9a. Exfoliating maxillary left deciduous tooth which has caused chronic bleeding in a 9-year-old severe hemophiliac (Factor VIII level less than 1%, *with an inhibitor*.) 9b. Immediately postoperatively the shallow extraction site of the tissue-borne tooth reveals no significant bleeding. The patient had received no Factor VIII replacement prior to the procedure, nor at any subsequent time. 9c. Application of topical thrombin directly to the tissue of the shallow extraction site. 9d. Preparation of the Stomahesive® "intraoral bandage" to protect the extraction site.

Following extraction of permanent teeth, local measures utilizing hemostatic agents (Avitene,® Topical thrombin, Surgical®) are important in controlling hemorrhage. Such local measures enhance the formation of a stable clot. The technique of packing a socket is important; the hemostatic agent should be positioned in the apical third of the root socket. In case of multirooted teeth, each individual root socket is packed separately. If oxidized cellulose is employed it is cut to size and is then impregnated with a thrombin solution (27). Prior to placing the thrombin saturated agent, the root socket is cleaned of any small clot that may have formed. The hemostatic agent is placed *directly against the bleeding area*, acting immediately to convert the fibrinogen of the blood into a fibrin clot which forms a plug in the socket. (Fig. 10a, b)

Despite all precautions secondary bleeding may occur, usually on the third or fourth postoperative day when the clot begins to break down. Such bleeding must be treated vigorously—*both systemically and locally*. Sufficient replacement factor must be administered to achieve a hemostatic level to control any prolonged bleeding which has reactivated. The idea of protecting a loose clot is discouraged. Added packing will never reach the source of bleeding which will continue beneath the clot. The typical clot in this situation is characterized as a "liver clot"—dark red, protruding from the surgical site, and often covering the surfaces of several teeth (Fig. 11). Following an adequate factor infusion any friable or loose clot should be removed and the site debrided to localize the exact point of bleeding in the surgical area. After isolating the source of bleeding, the socket should be repacked. The use of hemostatic agents in the treatment of hemorrhagic patients has not led to any

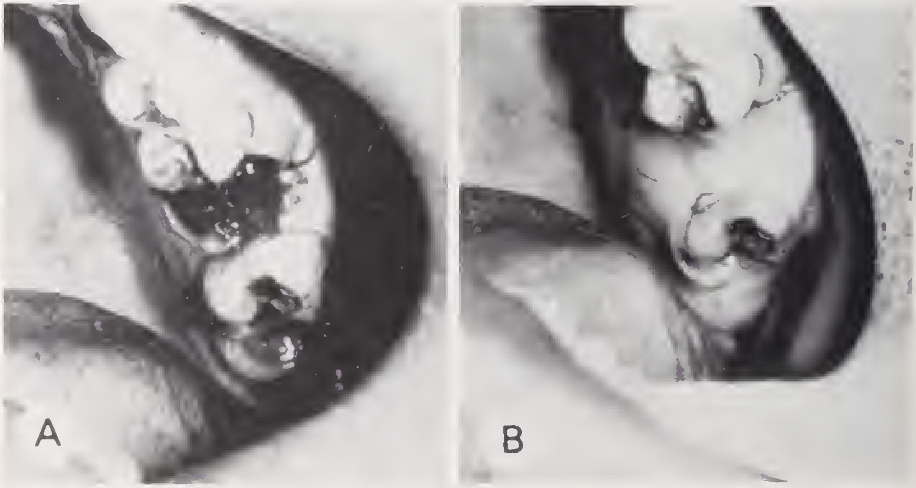


Fig. 10a. 30-year-old Factor VIII less than 1% patient immediately following extraction of two maxillary molar teeth. The extraction sites were packed with topical thrombin and Surgicel and sutured. 10b. Extraction sites immediately following placement of a Stomahesive bandage cut to size to protect the site for the first 24–36 hours.

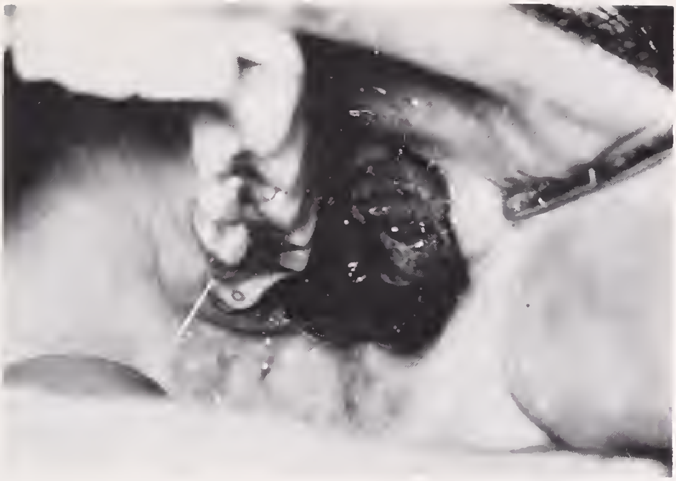


FIG. 11. A large clot formed four days following extraction of a maxillary third molar tooth in a 24-year-old patient, Factor VIII less than 1%. This patient had been maintained postoperatively on insufficient intermittent Factor VIII replacement. The clot was removed and the area treated locally in conjunction with replacement therapy to arrest the bleeding at the base of the clot.

significant postoperative complications involving delay of healing or infection. When infection is present at any extraction site, antibiotics may be indicated two days prior and three days after surgery.

Our experience has shown that sutures may be needed for extractions to reposition mucoperiosteal flaps, but should not be used as "tension" sutures. Suturing can also function to stabilize the hemostatic packing and protect it from being dislodged from the socket. When nondissoluble sutures are removed approximately a week postoperatively, bleeding is usually insignificant. If sutures are employed the surgeon should use a technique that does not exert excess tension and should avoid tearing weakened soft tissues.

Unless surgical stents are perfectly designed and fabricated, they usually create more problems than they are intended to solve and we do not recommend them. A cellulose bandage (Stomahesive®) can be cut and shaped around the teeth adjacent to the extraction site to protect the area initially while the clot stabilizes. (Figs. 10a and 10b) Such an intraoral bandage lasts for only 12–48 hours. To further protect the site and clot, diet is restricted to fluids initially and then soft foods prior to resumption of normal diet.

Emergencies in the Mouth

Oral trauma is especially common during childhood. Management of emergencies in the mouth of the hemophiliac requires a combination of local measures and systemic replacement therapy where indicated because of bleeding which is evident or suspected (19). Bleeding associated with trauma to the teeth is best controlled by systemic infusion of the missing factor to a level of 30–40%, the surgical hemostatic level, for 1 to 3 days.

Accidents involving the mouth range from fractured teeth, to bruises, hematomas, lacerations, and to multiple injuries involving the facial bones. Protruding maxillary incisors are frequently susceptible to injury (28). It is not always possible, nor is it necessary today to limit the physical activity of the hemophiliac. There are few precautions to take with the very young hemophilic child; older hemophiliacs are encouraged to participate in physical activity, avoiding only the roughest body contact sports.

An erupted permanent tooth, injured with only loss of enamel, should have its sharp edges smoothed and should be observed regularly. Traumatic injuries resulting in loss of tooth structure and exposed dentin require medicated dressings and protective restorations such as an orthodontic band or acrylic or stainless steel crown.

Traumatic injuries resulting in exposure of the pulp may require endodontic therapy of the teeth. In children, pulpotomy removes infected tissue, will allow healing to take place, and permits the apex of the tooth to approach complete development of root length and periapical structures. Infusion therapy may not be required if there is no bleeding. All patients should receive immediate symptomatic care, with definitive follow-up care.

To save a tooth which has been loosened or fractured, the dentist may have to splint the tooth in position. Endodontic therapy is often performed prior to replacing an avulsed tooth in the jaw. If bleeding is minimal the situation may require no replacement transfusion therapy.

For severe bleeding injuries in or near the mouth, pressure should immediately be applied directly over the wound. A combination of systemic replacement therapy and local measures is necessary to manage oral lacerations. The fluid environment (saliva) and routine mechanical action of swallowing and mastication often interfere with local management of such problems in the oral cavity. Initially sutures are effective to control intraoral bleeding. After hemostasis has been established (24–36 hours) it is advisable to remove the sutures. Sutures left in place can be easily pulled; the wound can be torn open, with bleeding reinitiated. Our experience with bleeding and intraoral lacerations has emphasized the importance of continuing systemic replacement therapy beyond initial hemostasis, to prevent a cycle of repeated secondary hemorrhages. Antifibrinolytic therapy can also be utilized. (Fig. 12)

Acute infections are painful and dangerous. The acute alveolar abcess and the chronic infection with fistula are common in the deciduous teeth of the pedodontic patient. Alveolar abscesses in children usually remain localized, although a cellulitis may develop in some situations. The chronically involved tooth is usually sensitive to percussion and an abnormal radiolucency may be evident on x-ray. Chronically infected teeth and acutely infected teeth which have been brought under control may respond to conservative endodontic therapy.

The patient who presents with an acute intraoral abcess of dental origin

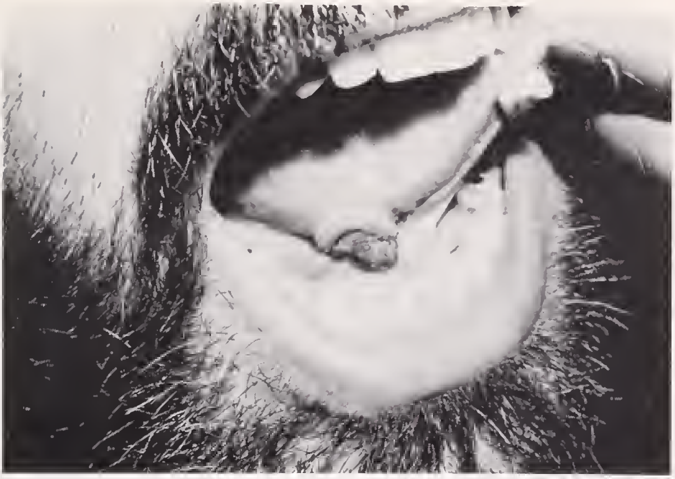


FIG. 12. This patient had inadvertently bitten the underside of his tongue. He had resisted treatment until bleeding had continued for four days, resulting in significant enlargement of the laceration. This view shows the enlarged lesion three days *after* hemostasis had been effected with systemic transfusion and antifibrinolytic therapy.

must have his acute symptoms relieved by an incision and forced drainage of the lesion, followed by warm saline rinses to avoid the rapid development of cellulitis. He should be protected by an appropriate antibiotic such as penicillin or erythromycin after cultures have been taken. Nonaspirin-containing analgesics should also be prescribed when indicated. The hematologist should be notified prior to treatment. Factor infusion to maintain the surgical hemostatic level of 30–40% is indicated. The patient must be carefully observed for the first 24 hours. One preoperative infusion of factor material may be sufficient to manage any bleeding associated with incision and drainage, but proper management must include the possibility of additional infusion of factor concentrate or cryoprecipitate where indicated.

Pericoronitis and necrotizing ulcerative gingivitis occur with the same frequency as among non-hemophiliacs and are managed with the same treatment as for non-hemophiliacs.

An emergency dental episode may be an isolated incident for some hemophilic patients. For many patients, however, it may be a symptom of chronic underlying dental neglect. Hemophiliacs who present needing general dental treatment, in addition to emergency treatment, must be strongly urged to seek good dental care once the emergency situation has been brought under control.

Summary

The hemophilias are congenital sex-linked recessive disorders caused by deficient activity of coagulation Factors VIII or IX which are necessary for normal blood clotting. Replacement therapy developed in the last decade has made possible the control of even the most severe bleeding in hemophilia.

No routine dental procedures involve bleeding; consequently, there is no contraindication to routine dental treatment for hemophiliacs. Aspirin should never be prescribed. Caution must be exerted with local anesthetic block techniques. Preventive dentistry is vital to the younger hemophiliac; older hemophiliacs may require extensive treatment to restore mouths which have suffered from years of neglect. Surgical dental procedures are now considered possible for hemophiliacs and may be performed on an outpatient basis, but they must be judiciously coordinated by the dental and medical team. There should be no compromise in the quality of dental care for the hemophiliac.

SECTION II

1975–76 Evaluation of Dental Program at Mount Sinai

The Mount Sinai Medical Center has a recognized tradition in treating patients with the hemophilia disorders and is designated one of the International Training Centers for Hemophilia. The evolution of the Mount Sinai Comprehensive Care Hemophilia Clinic has produced a facility which serves as a model for total management of chronic disease patients. The team concept includes an oral surgeon who supervises a dental program which has developed as an outgrowth of the Hemophilia Clinic. The dental program has focused on:

1. Screenings and evaluation
2. Consultation and referrals
3. General dental treatment
4. Oral surgery (treatment and clinical research)
5. Treatment of acute dental problems

Quality dental care has become a very real goal for hemophiliacs. At Mount Sinai both the attending and training resident dental staffs play an integral role in the overall health care of hemophilic patients. The Hemophilia Clinic at Mount Sinai focuses on adult cases and cooperates with the pediatric Hemophilia Clinic at the New York Hospital-Cornell Medical Center. Pediatric dental cases are referred from New York Hospital to the Mount Sinai facility.

Older hemophilic patients have complex dental needs; often their oral health has been ravaged by years of neglect. These patients may require multiple and complex procedures to return their mouths to a healthy and stable condition prior to restoring their dentition. Such treatment may involve extractions prior to endodontic and periodontal therapy. Crowns and fixed bridgework, as well as removable partial prostheses and full dentures are often indicated. After restoration, such patients are enrolled in a prevention program to maintain their dentition and to limit further complications.

The younger hemophilic population usually requires less dental treatment; our primary goal with the younger group is enlisting them in preventive programs. Pediatric patients have their immediate problems managed with endodontic therapy, restorations, stainless steel crowns, interceptive orthodontics, and extractions. Following initial treatment, the patients are instructed in oral hygiene and placed in a program which monitors their preventive care and provides periodic checkups and maintenance care.

Review 1975–76 (Table I)

1. Screenings and evaluations. A dental history is obtained from all hemophilic patients who present to the Comprehensive Care Hemophilia Clinic and an oral screening is performed. (Table II) Where indicated for more in depth evaluation, dental radiographs are obtained.

2. Consultation and referrals. Patients are advised of their dental needs. Those patients actively receiving dental care are urged to continue ongoing treatment. Patients who are not under the care of a dentist have the choice of being referred either privately to practitioners who have been informed of the needs of hemophilic patients, or to the Dental Clinic of the Mount Sinai Medical Center. In either case it is the team oral surgeon who coordinates the dental care and who acts as direct liaison between the Hemophilia Clinic and the dentists rendering treatment. We prefer that our patients be treated privately whenever possible. We feel that this approach is more practical geographically for many of our patients, and, in addition, it removes the patient from the clinic and places him in a more normal environment.

3. General Dental Treatment. Only a limited amount of dental care is rendered in the weekly Comprehensive Care Hemophilia Clinic session essentially no treatment, but screenings, evaluations, referrals, supervision of current treatment, and coordination of projected treatment. Since dental

TABLE I

Statistical Breakdown of Oral Surgical Services Rendered 1975–76

1a.	Oral Examination and Screenings	69
1b.	Radiographic Examinations/Evaluations	62
2.	Referral Consultations	25
3a.	Oral Surgical Cases	19

Procedures	Inpatients	Outpatients	Totals
Adult Extractions	48	5	53
Deciduous Extractions	2	2	4
Cyst Enucleation	1	1	2

3b. Clinical Research
(In 1975–76 eight of the Oral Surgical Cases were included in the Amicar® Study. No patients had as yet formally entered the Alcon Study.)

4.	Management of Dental Emergencies	18

TABLE II

Dental History Form Utilized by the Mount Sinai Medical Center International Training Center for Hemophilia

DENTIST: Name
Address
DATE OF LAST DENTAL TREATMENT:
CHECK BELOW TYPES OF DENTAL TREATMENT YOU HAVE RECEIVED IN THE PAST:

	YES	NO
X-Rays		
Cleaning		
Root Canal Treatment		
Orthodontic Treatment		
Fillings		
Crowns or Bridges		
Partial Dentures		
Full Dentures		
Extractions		
Oral Surgery		

IF YOU HAD EXTRACTIONS, PLEASE GIVE DETAILS:
When:
Where:
Oral Surgeon:
What treatment products did you receive?
Have you received adjunctive agents (i.e., Amicar)?
DO YOU NEED TO BE REFERRED FOR DENTAL TREATMENT NOW?
CURRENT DENTAL EVALUATION:

			e	d	c	b	a	a	b	c	d	e			
8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
			e	d	c	b	a	a	b	c	d	e			

treatment is performed outside of the weekly Comprehensive Clinic there is constant need for follow-up and reinforcement of ongoing treatment. A concentrated effort is made to recruit patients suffering from dental neglect and to initiate them to a program of rehabilitative dental care.

When patients are referred to the Mount Sinai Dental Clinic, all phases of general dental treatment are available. (Table III) Since there is no bleeding from general dental procedures, patients are rarely hospitalized for general dental work and are routinely treated as outpatients. Problems and complications are screened by the oral surgeon and by the Comprehensive Clinic Team where necessary.

4. *Oral Surgery.* Patients who present to the Comprehensive Clinic requiring oral surgery (usually dental extractions) are primarily supervised by the oral surgeon either as inpatients or as outpatients in the Mount Sinai Oral Surgery Clinic. (Table I) Those patients who meet the criteria of ongoing clinical research and who are willing to participate are enlisted in an appropriate study. (Currently there are two studies in progress:

1) EACA-Amicar® the antifibrinolytic drug Epsilon Amino Caproic Acid.

TABLE III

Proposed Program for the Comprehensive Hemophila Dental Treatment Center at the Mount Sinai Medical Center

- I. Department of Dentistry Staff
  - A. Oral Surgeon Coordinator
  - B. Attending General Dentists
  - C. Specialty staffs:
    - 1. Pedodontia
    - 2. Endodontia
    - 3. Orthodontia
    - 4. Periodontia
    - 5. Prosthodontia
    - 6. Oral Surgery
  - D. Dental Residents (Monthly assignment)
  - E. Oral Surgery Resident (2nd year resident monthly rotation)
  - F. Dental Hygienists
  - G. Oral Surgery R.N.
  - H. Dental Assistants
- II. Hemophilia Center:
  - A. Clinic
  - B. Lectures
  - C. Conferences
- III. Dental Treatment
  - A. Dental Procedures
    - 1. Patient history and physical evaluation
    - 2. General Dental and oral examination
    - 3. Radiographic survey and evaluation
    - 4. Treatment planning
    - 5. Preventive dental care
      - a. Prophylaxis and scaling
      - b. Home care instruction – toothbrushing
        - flossing
        - water irrigating
        - diet
        - fluoridation
      - c. Recall – follow up care
      - d. Caries control
    - 6. Endodontic therapy
    - 7. Pedodontics
    - 8. Orthodontics
    - 9. Operative dentistry
    - 10. Prosthetics
  - B. Surgical Procedures (including Periodontics)

2) Microfibrillar Collagen Hemostat - Avitene® a topical hemostatic agent.)

5. Acute Dental Problems. Bleeding in the mouth and acute dental problems (i.e., abscess, toothaches) are handled on an emergency basis. Patients contact the Hemophilia Clinic, or directly contact the oral surgeon.

Dental Training Program for Hemophiliacs

The ideal dental program for hemophiliacs should be a treatment program as well as a *teaching vehicle*. The training part of our program is undergoing constant expansion and involves the professional attending staff, resident house staff, and ancillary personnel. (Table III) Professional dental attending staff includes the general dentists as well as specialists in pedodontics, orthodontics, endodontics, periodontics, prosthodontics and oral surgery. General dental residents are all becoming involved in the delivery of dental care to hemophilic patients. They are assigned on a monthly basis to rotate through the Comprehensive Care Clinic where they participate in a varied program including lectures, conferences, and clinical training sessions. The residents in the three-year oral surgery training program and residents in the dental anesthesia program rotate in the Hemophilia Clinic and assist in rendering oral surgery and anesthesia management to the patients. Dental and oral surgery residents are also involved in ongoing clinical research programs, supplementing the development of their clinical skills. In addition, as an extension of the International Training Center for Hemophilia, the dental component has been observed by a number of delegates and will receive an oral surgery fellow from Brazil in 1977.

The immediate benefits of delivery of such specialized care by house staff and attendings are obvious. Additionally, there are longer term advantages and far reaching effects of training personnel who will eventually be capable of providing dental and oral surgery treatment for hemophiliacs in other geographic locales. The Mount Sinai dental attending staff is drawn from New York City and State, from Connecticut and from New Jersey, constituting a widely spread group of practitioners exposed to the delivery of dental care for hemophiliacs in the private sector.

We are currently attempting to involve the dental hygiene staff more significantly, particularly in conjunction with the periodontal department in implementing the preventive dental care program. The role of a hygienist is vital for:

1) rendering treatment
2) supervising the prevention program
3) acting as buffer between patients and the threatening image of the dentist.

Similarly, the oral surgical nursing staff is intimately involved with the management of patients undergoing extractions and surgical procedures. Beyond the immediate teaching environment of the Hemophilia and Dental Clinics, team members are actively involved on local, regional, national and on international levels. Representatives from the dental department have reported on advances in dental treatment for hemophiliacs at conferences and symposia: New York, New Jersey, Washington, Pennsylvania, Kentucky; Helsinki; Moscow; Costa Rica; Brazil and Japan. Currently, publications generated from the department are in press including contributions to the dental manual in the series *Treatment on Hemophilia* sponsored by the National Hemophilia Foundation. We consider the teaching efforts of our program vital and significant.

Financial Considerations

Despite a comprehensive dental program, economics have severely limited our delivery of care to hemophilia patients. Although we find that the disease process no longer restricts the dental care possible for our patients, we do find that we must often compromise ideal dental care because of financial restrictions.

Complete oral surgery treatment is made available for all patients; however, most of the care rendered by the voluntary oral surgeon is classified as "dental treatment" and is not reimbursable by third-party programs. A good number of patients cannot afford private general dental care, but at the same time are ineligible for Medicaid reimbursement. Consequently the general dental treatment program has not been able to provide totally ideal care because it is not self supporting, nor is it subsidized.

Conclusion

Our dental experience at Mount Sinai has involved the two areas of general dental treatment and oral surgery. The result of our general dental efforts is documented in the recommendations and treatment philosophy as put forward in Section I of this paper. The statistics of our surgical experience in Table I are further developed in *Oral Surgery* in Section I.

We are pleased with some of the developments of our dental program for hemophilic patients at Mount Sinai, particularly in the areas of oral surgical procedures and research and of evolving general dental treatment possibilities and goals for those patients. Additionally, we feel that we have made significant progress in the education and motivation of our *patients and their physicians* regarding their dental health, and that we have achieved a certain level of educating *dentists* in the treatment of patients with hemophilia.

Although we are aware of the many and varied dental needs of hemophilic patients, we are hard pressed to provide for them all the dental care they require. In 1977 the management of the disease hemophilia has evolved to a point where all aspects of dental care should be available for these patients. Unfortunately, because of economic and personnel limitations, we find that our program has not yet achieved the ideal dental care these patients deserve.

Rules of the Game

1. *Do Not be Afraid of Bleeding*
   A hemophiliac does not bleed any *faster* than a non-hemophiliac. A hemophiliac bleeds for a longer time due to a defect in the clotting mechanism. No hemophiliac will exsanguinate on the spot.
2. *Be familar* with the type and severity of the hemophilia of your patient. Usual replacement therapy is contraindicated for patients with *inhibitors*.
3. *Consult* with the patient's physician and hematologist.
4. Infiltration anesthesia should be used with caution. Block anesthesia must be used with extreme caution even with replacement therapy.
   Positive aspiration or a hematoma will require further treatment.
5. *Aspirin*. Never prescribe aspirin or aspirin-containing compounds to a patient with a bleeding disorder. They will affect platelet aggregation and thus exaggerate the bleeding defect.
   Use a substitute analgesic such as Tylenol, Codeine or Meperidine.

6. *Protect* soft tissues. Care must be taken with the high speed vacuum and saliva ejector to avoid causing a sublingual hematoma.
   Care must be exercised to avoid laceration of the lip or tongue with dental instruments and drills.
   Care must be taken with the placement of x-ray films.
   Care must be taken when taking impressions; line periphery of the tray with wax.
7. *Avoid* intramuscular injections for hemophiliacs who have not received replacement therapy.
8. Hemophiliacs who have been receiving blood products may be carrying the hepatitis virus. All instruments should be *autoclaved.*
9. *Never compromise quality dental care.*

References

1. Dunning, J. M.: Incidence and Distribution of Dental Caries in the United States, Dent Clin N Amer July, 1962:291.
2. Webster, W. P., Robert, H. R., and Penick, G. D.: Dental Care of Patients with Hereditary Disorders of Blood Coagulation, Modern Treatment 5:93, 1968.
3. Walsh, P. N., Rizza, C. R., Evans, B. E., and Aledort, L. M.: The Therapeutic Role of Epsilon Amino Caproic Acid (EACA) for Dental Extractions in Hemophiliacs, Ann NY Acad Sci 240:267, 1975.
4. Biggs, R., Mathews, J. M., Rush, B. M., Johnstone, F. C., MacFarlane, R. G., and Hayton-Williams, D. S.: Further Experience in the Use of Human Anti-Haemophilic Globulin (H.A.H.G.) for the Control of Bleeding after Dental Extraction in Haemophilic Patients, Lancet 1:606, 1965.
5. Eys, J. V., Agle, D. P., Hilgartner, M. W., and Lazerson, J.: *Home Therapy for Hemophilia: A Physician's Manual*. Medical and Scientific Advisory Council, National Hemophilia Foundation: June, 1974.
6. Levine, P. H. and Britten, A. F. H.: Supervised Patient Management of Hemophilia, Ann Internat Med 78:195, 1973.
7. Levine, P. H.: Efficacy of Self-Therapy in Hemophilia: A Study of 72 Patients with Hemophilia A and B, N Engl J Med 291:1381–1384, 1974.
8. Aledort, L. M.: The Management of Hemophilia: A Perspective, *Drug Therapy*, March 1971 Vol 1 No. 3.
9. Evans, B. E.: Comprehensive Dental Treatment for the Hemophiliac. Proceedings of the 2nd International Meeting on Hemophilia and the Latin American Meeting on Blood Transfusion and Plasmapheresis. San Jose, Costa Rica, January 20, 1975.
10. Walsh, P. N.: Epsilon-Aminocaproic Acid Therapy for Dental Extractions in Haemophilia and Christmas Disease: A Double Blind Controlled Trial, Br J Haematol 20:463, 1971.
11. Mulkey, T. F.: Outpatient treatment of Hemophiliacs for Dental Extractions, J Oral Surg 34:428, 1976.
12. Needleman, H. L., Kaban, L. B., and Kevy, S. V.: The Use of Epsilon-Aminocaproic Acid for the Management of Hemophilia in Dental and Oral Surgery Patients J Am Dent Assoc Vol 93: Sept. 1976.
13. Lucas, O. N. and Prescott, G. H.: Hemophilias and Other Hemorrhagic Disorders: Significance of Preventive Dentistry, Dent Clin N Amer 19(1):63, 1975.
14. Nazif, M: Local Anesthesia for Patients with Hemophilia, J Dent Child 37:79–84, 1970.
15. Evans, B. E.: Hemophilia Symposium: Current Concepts of Treatment and Management. Moscow, U S S R August 4, 1975.
16. Berger, S. and Aledort, L. M.: The Use of Analgesics and anti-Inflammatory Agents in Hemophilia. *Handbook of Hemophilia* Edited by K. M. Brinkhous and H. C. Hemker, Excerpta Medica, Amsterdam, 1975.

17. Lucas, O. N.: Dental Extractions in the Hemophiliac: Control of the Emotional Factors by Hypnosis, Amer J Clin Hypnos 7(4):301–307, 1965.

18. Lucas, O. N.: Hypnosis and Stress in Hemophilia. The hemophiliac and His World. *Proceedings of 5th Congress of World Federation of Hemophilia*, Montreal, August 1968.

19. Evans, B. E.: Dental Management In *Hemophilia in Children*. Edited by M. W. Hilgartner. In the series: *Progress in Pediatric Hematology-Oncology*, J. Wiley and Sons. Publishing Sciences Group Inc. Littleton Mass. 1976, pp. 109–135.

20. Chiono, O. and Miyamoto, O.: A Comprehensive Pedodontic Program for Hemophiliacs. *Proceedings of the Dental Hemophilia Institute*, Chapel Hill, North Carolina, University of North Carolina, January 19–20, 1968.

21. Nakai, T. R., Peterson, J. C., and Law, D. B.: Current Concepts in the Management of the Hemophilic Pedodontic Patient, J Dent Child 41(5):361, 1974.

22. Bjorndal, A. M.: Endodontic Treatment of an Upper First Molar in a Hemophiliac, Oral Surg Oral Med Oral Pathol 14:472–473, 1961.

23. Evans, B. E. and Aledort, L. M.: Preliminary Report on the Therapeutic Role of Epsilon Amino Caproic Acid (EACA) for Dental Surgery in Hemophiliacs. The Tenth Congress of the World Federation of Hemophilia. Helsinki, Finland, July 31, 1975.

24. Birch, C. L.: *Hemophilia, Clinical and Genetic Aspects*. University of Illinois Medical and Dental Monographs 34:60, March 1937.

25. Abbott, W. M. and Austen, W. G.: Microcrystalline Collagen as a Topical Hemostatic Agent for Vascular Surgery, Surgery 75:925, 1974.

26. Hunt, L. M. and Benoit, P. W. Evaluation of a Microcrystalline Collagen Preparation in Extraction Wounds, J Oral Surg 34:407, 1976.

27. Lucas, O. N.: Use of Oxidized Regenerated Cellulose Saturated with Thrombin $NaCHO_3$ Solution To Effect Hemostasis in Exodontia, J Canad Dent Assoc 32:146–153, 1966.

28. Shusterman, S.: Treatment of Class III Fractures in the Hemophiliac Patient: A Case Report, J Acad Gen Dent 21(6):25–28, November-December, 1973.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May-June, 1977
Printed in U.S.A.

Psychosocial Aspects of Hemophilia: Problems, Prevention, Treatment Modalities, Research, and Future Directions

ELIZABETH WINCOTT, A.I.M.S.W.

The entry of a hemophiliac into a family profoundly and irrevocably alters the lives of the parents, siblings, close family members, and friends. This event is superimposed on an already existing pattern of personalities and family interrelationships. Their ability to cope depends on these factors and the part played by health care professionals both at the time of diagnosis and throughout the life of the hemophiliac. Katz (1) and others have observed that the problems encountered are for the most part similar to those in any chronic hereditary condition with some additional special features, in particular, the constant concern regarding the threat of traumatic and spontaneous bleeding.

Helping the patient and family reach acceptance of their situation and in turn to function as fully and freely as possible both physically and emotionally is the goal of all treating personnel. Mental health professionals on the hemophilia care team are especially concerned with emotional functioning. Agle (2, 3) refers to the importance to the hemophiliac of having a sense of mastery of himself and his treatment. This is in part achieved by "the child's understanding of his illness (which permits him to use his own judgment in controlling his activity rather than limit it, because of fear" (2).

This paper will outline some of the emotional and social problems encountered by the hemophiliac and his family, and discuss how these may be handled by various therapeutic modalities. The particular issues confronting the hemophiliac and his family at milestones in his life will be looked at from a longitudinal perspective. Finally, gaps in current knowledge with recommended directions for treatment and research will be highlighted, particularly in relation to an expanded view of the social work role.

The concept of comprehensive care can be interpreted in a variety of ways. The Mental Health Committee of The National Hemophilia Foundation recently held a workshop at which, among other concerns, various applications of the comprehensive care model were initially developed and reviewed. The goal is to meet a diversity of local needs through flexible application of the model. Broadly speaking, comprehensive care centers are set up so that an individual is treated not only for a particular disease but also for his total social health care needs. For example, the Mount Sinai Hemophilia Team, which meets weekly, includes hematologists, laboratory technicians, an orthopedist, psychiatrist, physical therapist, oral surgeon, physiatrist,

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From the Department of Social Service, The Mount Sinai Hospital, New York, N.Y. 10029.
Requests for reprints should be sent to: Elizabeth Wincott, A.I.M.S.W., Department of Social Services, The Mount Sinai Hospital, Fifth Avenue and 100 Street, New York, N.Y. 10029.

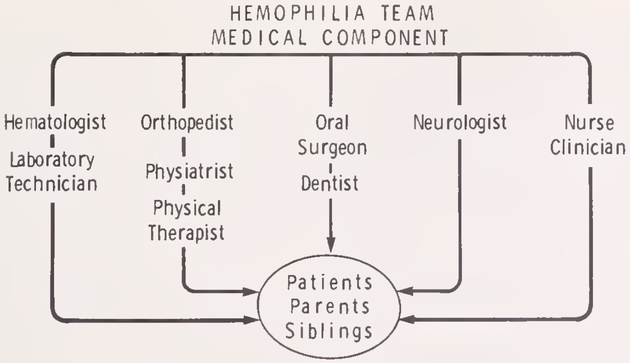
HEMOPHILIA TEAM
MEDICAL COMPONENT
Hematologist
Laboratory Technician
Orthopedist
Physiatrist
Physical Therapist
Oral Surgeon
Dentist
Neurologist
Nurse Clinician
Patients
Parents
Siblings

Fig. 1.

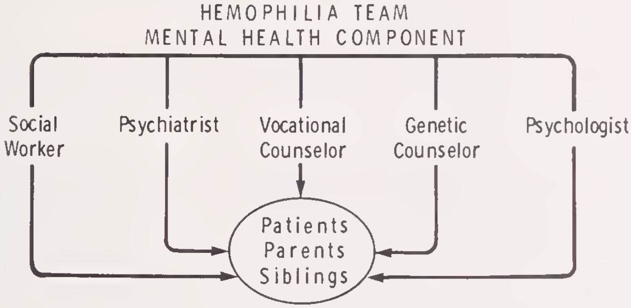
HEMOPHILIA TEAM
MENTAL HEALTH COMPONENT
Social Worker
Psychiatrist
Vocational Counselor
Genetic Counselor
Psychologist
Patients
Parents
Siblings

Fig.2.

nurse clinician, vocational counselor, neurologist, and social worker (See Figures 1 and 2). It has been found that the quality of care as perceived by the treating personnel and patients is felt to be markedly better in a total care setting where each of the personnel has particular expertise regarding the disease he is treating (4, 5). In this type of setting, the hemophiliac and his family are seen as a unit in the context of the patient's total life situation. The comprehensive care team members, in interchange and sharing, enhance each other's perspective and engage in better ongoing communication on behalf of the patient, enabling a clearer delineation of short and long term goals.

Experience has shown that in the many instances where hemophiliacs are treated by physicians who see perhaps one or two such patients in their career, or in hospitals which are not familiar with hemophilia, there is considerable ignorance and fear that is detrimental to the hemophiliac and his family. Negative and hostile attitudes resulting from ignorance are often encountered, particularly in emergency rooms.

Early intervention, preferably at the time the diagnosis is made, is of paramount importance. Hurt (6) states that with "early brief term treatment and followup, a great majority of individuals function within normal limits despite the many complications imposed by the disease." Since the late 1950's physicians and individuals in mental health services have been pointing to the need for increased attention to the psychosocial problems of hemophilia. The last decade has seen tremendous advances in the understanding of the hematologic aspects of the disease and the development of factor concentrates. Although there is an increased concern with psychosocial issues (1, 7) and the knowledge base is expanding, hard data from research in this area are still lacking. Not only are physicians such as Brinkhous, (7) a professor of pathology, calling attention to the need for psychosocial services, it is interesting also to note that Petit and Klein (8) of the National Heart and Lung Institute, in a study for the Department of Health, Education and Welfare have, in delineating health care needs for hemophiliacs, drawn heavily from information viewed from the social standpoint. Factors taken into account included financial disability, education, discrimination by employers, marital difficulties and emotional problems. They stressed the importance of the roles of each of the hemophiliac center personnel in maximizing effective utilization of the health care system.

In making an initial evaluation of a patient and family during the first visit to a comprehensive care clinic the following psychological and socioeconomic picture is determined in order to make an evaluation of the individual's and family's needs in these areas. At the first visit, or in a subsequent visit within a few weeks, the team members hold a conference to present their recommendations for the treatment of the individual. In making such a plan account is taken not only of the medical needs but also the geographical location of the patient in relation to his accessibility to the hemophilia center or other appropriate facilities. Where necessary, an attempt is made to fit the treatment plan into the school year; for example, when elective surgery needs to be done or an intensive course of physical therapy is indicated, it is scheduled, where possible, during a vacation in order not to disrupt the school year. When a hemophiliac is employed, his job demands and the flexibility of his employer are considered with regard to time off. At the second visit, when recommendations are made to the hemophiliac and his family, there is also an opportunity for further interchange with the family. It is essential to begin to involve the total family from the outset. They need to understand the nature of the disease and begin to have some awareness of its impact emotionally—both intellectually and at a feeling level—so that they can begin to develop coping techniques. We want them to become participants in treatment from the beginning. This type of evaluation and early planning is only possible in a comprehensive care approach since it provides the means for effective communication and a greater understanding of each team member's role. Each can call in another more smoothly and easily when a need is perceived if good professional collaboration already exists. Current patient activities and problems, particularly when home therapy is being monitored, should be coordinated by one team member, who would in addition serve as liaison to clinic members. Ideally, this strong "link" person should be a nurse clinician. If such a person is not available on a full-time basis the role has, in some centers, been undertaken by the social worker who can function effectively in this capacity because of her particular understanding of the patient and family's total situation and needs. One of the contributions of the social worker to the care of the hemophiliac is to highlight the need to examine the psychosocial impact of hemophilia on the patient and his family, and conversely the way in which family and environment affect the course of the disease. For example, an adolescent who displayed severe emotional problems was diagnosed as a sociopath. His major behavioral problems prevented him from entering into a treatment plan or continuing with schooling. The social worker together with an orthopedist who had been working with the boy, saw the patient's mother in a joint session. It was felt that in order to be of help, it was important to have a better understanding of the boy and his family. The boy's inner and outer resources posed real limitations. At that time the family was not seen regularly since the boy attended clinic on his own. This session enabled the social worker and physician to have a better understanding of the severe limitations of the home environment, and it was concluded that there could be no greater expectation of the boy's potential. Many attempts were made to include the total family in a contract to work on the treatment plan, but because of their overwhelming rejection, this was unworkable.

As previously mentioned, early intervention by all team members is essential. Factual information about the disease entity given to new parents makes for a much smoother and more rapid adjustment. Functioning of the couple is assessed by each of the mental health professionals and intervention is then directed toward working with their ego strengths and existing environmental supports. For example, a family from out of town was seen at the Mount Sinai Clinic for an evaluation of their 12-year-old son. This informed and extremely well-adjusted family had, through the help of professionals and their own efforts, become aware of the illness and its implications. Since communication within this family was good, they had been able to share this with their son, and thus derived much mutual support. It was impressive to all those who saw this family that early information and support was the key factor in their successful adjustment.

Social Diagnosis and Assessment (see Figure 3)

Following are the areas that should be identified by the social worker in an initial interview with the hemophiliac and his family in the case of a child or an adolescent.

1. *The Family.* Family structure, family interrelationships, their concept of family, strengths and weaknesses, the involvement of the extended family, the impact of the knowledge of hemophilia on the patient and the family. Previous family history of hemophilia and their understanding of this, their expectations of the center, since some patients and families can have a distorted and unreal expectation of what can be done for them. A number of people have highlighted the importance of the family, and especially parents, in the healthy and successful adaptation of the hemophiliac. Various authors (9, 10, 11) have commented from a variety of perspectives, but certain common themes emerge, such as the extreme importance of the parents jointly being involved in raising and disciplining the child.

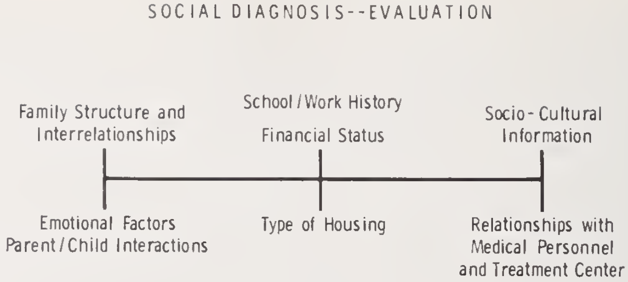
SOCIAL DIAGNOSIS--EVALUATION
Family Structure and Interrelationships
School/Work History
Financial Status
Socio-Cultural Information
Emotional Factors
Parent/Child Interactions
Type of Housing
Relationships with Medical Personnel and Treatment Center

FIG. 3.

2. *Emotional Factors.* An evaluation of the patient and family's emotional functioning, patterns of dependence and independence; special tensions and stresses within the family, and patterns of protectiveness are evaluated. It is vital that the parents understand their separate and unique reactions to the fact that the mother has produced a child with a defective gene. If not helped to deal with these feelings, frequently a guilty mother will isolate herself and the father will blame her and withdraw.
3. *School, Work, and Finances.* Patient and family's work situation, educational background, economic status, and sources of income are all important in understanding and evaluating the family's potential for coping. Stability of work, and economic status are particularly important in the case of hemophilia since the cost of treatment, especially of blood products, is enormous. Possibilities of retraining are explored when the work situation is unsatisfactory or the patient is unemployed. Information is gained on insurance coverage since many policies are archaic and do not cover the essential needs of the hemophiliac, in particular the cost of blood products. Special needs in education, vocational training and employment have been investigated in several studies (15–19).
4. *Housing.* The housing situation and type of neighborhood in which the family lives are significant. Since, for example, a hemophiliac who has severe hemarthrosis and who lives in a walk-up or has stairs to climb to reach his door suffers a severe handicap. This has been identified as a difficulty in Great Britain. Boone and Roberts (4) noted that in a survey of 137 hemophiliacs in Northern England, 6 of these had severe housing problems and the social worker was able successfully to help in rehousing these families. Markova (20) conducted a study in Scotland that provided information about the type of housing and numbers of stairs, distance from transportation, and so on. Although studies have not mentioned this problem in the United States, this center has a number of patients who have had housing problems.
5. *Sociocultural Data.* Knowledge of peer group relationships, hobbies, religious and social affiliations, ethnic and cultural background, use of community resources and association with a local hemophilia organization are all necessary in gaining a complete understanding of the family.

6. *Health*. The general health picture of the whole family and the history of their previous contacts with doctors and hospitals is reviewed. It is the experience of this social worker that hemophiliacs and their families who have had good previous experiences can adjust to a new center much more quickly than patients who have had little or no contact, or poor previous experiences. Frommer and Ingram (5) have stressed the importance of a good relationship between patients and their doctors. They also indicate that fewer difficulties exist when patients attend a center. An assessment of the history of hospitalization and contacts with hospitals and clinics prior to coming to this center is made. How hemophilia has affected the school child's ability to remain in school, and in the case of the adult, whether he has been able to continue his work and the effect on family relationships of periods of disability is also ascertained. The effects on areas of social functioning are viewed dynamically in the context of the patient's health history and current status.

The collation and interpretation of this information to members of the team plays an important part in formulating a treatment plan. The functioning of the patient and his family is a dynamic process; hence, there can be changes in stresses that the hemophiliac and his family experience at any given time and therefore reevaluation can be indicated. As previously mentioned, it is important that the patient and family share in this assessment and planning process and at the same time the social worker evaluates the ability and willingness of the family to enter into and become involved with a particular treatment plan.

Favre-Gilly (21), stating the importance of preventing "social crippling" viewed potential social and economic problems from the perspective of milestones in a child's life (Fig. 4). This longitudinal view is especially pertinent when dealing with chronic genetic disorders; and it has been used by Mattsson and Gross (14) and others. This approach anticipates potential problems and facilitates the possibility of dealing with them pre-crisis.

1. *Infancy*. As previously mentioned, the ideal time for intervention by a comprehensive care team is at the point of diagnosis, which very often in the case of a severely affected individual is at circumcision. It is important at this time to begin to present the complete and accurate medical facts. Initially, parents may be shocked, angry, guilty, sad and rejecting (12, 22, 23, 24). Parents need to be helped with these feelings in order to accept themselves and the entrance of this hemophiliac baby into their lives. It has been demonstrated (14) that some of the reactions commonly observed become useful adaptational and defensive techniques which assist the parents in their normal functioning in raising the child. When given the medical facts at the outset parents may be in such a state of shock that they need to be told several times over in a supportive and sympathetic atmosphere. Social workers and psychiatrists can be of great value in assisting the physician with this. Common reactions on the part of the mother at this time are to overprotect the child, isolate herself from her usual social contacts, and neglect her job and other children (21).

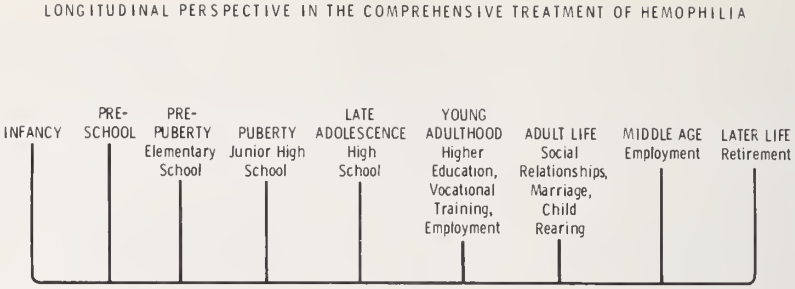
LONGITUDINAL PERSPECTIVE IN THE COMPREHENSIVE TREATMENT OF HEMOPHILIA
INFANCY
PRE-SCHOOL
PRE-PUBERTY Elementary School
PUBERTY Junior High School
LATE ADOLESCENCE High School
YOUNG ADULTHOOD Higher Education, Vocational Training, Employment
ADULT LIFE Social Relationships, Marriage, Child Rearing
MIDDLE AGE Employment
LATER LIFE Retirement

Fig. 4.

Many studies have indicated that fathers tend to blame mothers when they learn of the genetic inheritance and in some instances remain aloof or seemingly disinterested. Extreme cases have been reported where the father deserts the family. The experience of our center is that the burden of caring for the child falls very heavily on the mother. This may, of course, be in part due to the fact that the father is frequently the sole breadwinner and that it is hard for him to leave his job to bring his child to the treatment center.

The value of early education about the disease and its positive relationship to later successful adaptation has been stressed by a number of authors including Meyers (11). Hurt (9) suggests that "the father's active role in the family is the single most important factor" for emotional adjustment. Goldly and Katz (10) also stress the importance of the father's role but somewhat differently. In a study reported in 1963, well-adjusted hemophiliacs tended to look back and remember their fathers as being masculine individuals with whom they could identify, but these fathers very often were apparently indifferent and noninvolved during most of their son's upbringing. The above authors felt that indifferent fathers were seen as preferable to those who repeatedly denied their sons the opportunity to participate in physical activities. The restrictive, if well-meant attitude, engendered a great deal of resentment.

2. *Preschool*. During the preschool years parents are encouraged to express their concerns and fears about injury. Realistic limitations and medical problems are discussed with the social worker and the medical staff. In general the parents are encouraged to ventilate their fears and concerns and it is important to help them understand that however careful they are the child will have some bleeds. It is also important to help the parents find the balance between reasonable physical protection and physical and psychological "smothering." This particular problem has been referred to by almost every writer in the area of social and emotional adjustment. The social worker will also help the parents to begin to let their child make normal peer group contact which is an important part of the process of socialization. Wherever possible a nursery group or kindergarten is recommended. This is not only advantageous to the child but gives the mother her first and often much-needed respite.
3. *School*. It is the contention of this center that, with rare exceptions, it is

very important for the child to enroll in a normal school. This may involve considerable preparation with the parents in terms of dealing with their anxiety but also the center staff needs to reach out to schools and educate them about the disease. This educational role is very important and has been referred to by Jones (25). An effort to inform educators has been made by the National Hemophilia Foundation in a recent booklet (21) and by the Director of Social Service in the Michigan Chapter of the National Hemophilia Foundation (27). The question of normal schooling versus special schooling versus home tuition is controversial. Dormandy, Gandy and Britten (28), in a study reported in 1965, indicated more effective treatment and hence less time missed in school could be achieved in a special school. Respondents in their study frequently stated that they would have liked special school facilities. The National Health Service of Great Britain sponsors a boarding school; The Lord Mayor Treloar School at Alton, Hampshire, England. Allain (29) also reported in a later paper the good results obtained at a boarding school for hemophiliacs in France. "Far from implying that hemophilic patients should be permanently isolated from society, we think that a temporary stay in a boarding school provides a model for comprehensive care for hemophilic children." In contrast, Bronks and Blackburn, (19) in a questionnaire sent to 135 hemophiliacs, addressed themselves, among other issues, to the question of schooling. This study was carried out in the north of England and showed that the respondents who attended regular schools do as well and graduate at the same age as the general population. Why then were such differences found between two areas in Great Britain within a matter of three years of each other? This difference could in part be due to the different techniques employed in the study.

It is the firm contention of this center's staff that isolating a child, even temporarily, in a special school situation or keeping him at home on home tuition tends to emphasize his difference, foster dependency and overprotection, and therefore be an unfavorable influence when working toward a healthy social and emotional adaptation. Therefore the efforts of the whole clinic staff are frequently directed towards helping parents understand the benefits of their child remaining in or returning to school. This can be very hard for parents and very frightening, especially, as in the case of one seven-year-old boy seen in this clinic, when a series of hospitalizations was precipitated by an injury sustained at school.

The clinic saw one family that manifested a pathological degree of overprotection and the early indications of a symbiotic relationship between mother and son. The seven-year old child had, for over a year, remained essentially at home and bed-bound for no good medical reason. The need for hospitalization for wedge-casting to straighten a knee contracture was proposed. The mental health staff of the clinic needed to spend considerable time with the parents to help them verbalize their fears, understand the hospital structure and routine, and sense the support of the center staff. Following hospitalization, work with the parents was directed toward helping them separate somewhat from the boy, one long-term goal being that he should return to school. At the time of writing, this boy is now back in school and beginning to develop more normal peer group relationships. His mother, however, has taken a job as an aide in another classroom, since they have not yet reached the point where they can separate from him in an age-appropriate fashion. Partly because of lack of early comprehensive intervention and partially because of personalities involved, the existing patterns were already deepseated in this family and it was hard to help them make any significant changes.

From school age on, increasing attention is paid to individual work with the hemophiliac. Mattsson and Gross (14) and others have noted that from the age of 6 or 7, well-adapted patients can begin to comprehend the nature of the disease and to make a connection between physical trauma, bleeding, and treatment procedures. The more boys are able to be trusted to report injuries and cooperate in treatment, the more quickly they are able to adapt and begin to compensate for any physical limitations. Nonaggressive physical activities such as swimming, bicycling, and table games are often recommended, as are sedentary activities such as reading and building models. As indicated previously, ignorance on the part of schools often prevents them from making appropriate decisions as to where to place a child. It is the responsibility of clinic staff, and particularly the social worker, to coordinate information and education offered to school personnel (25). A patient seen at this center was found to be taking health conservation classes. The health conservation classes offered only basic courses in small groups; since many in the class were far behind in school work. The teaching is geared to the lowest denominator rather than individuals needs. His dissatisfaction with this limited program led him to truancy and interestingly, secretly joining larger normal classes. He was very eager to widen his curriculum and also to participate in physical education. The clinic staff encouraged him to pursue this and after several discussions with the school and a letter from the hematologist and orthopedist confirming that the boy could be involved in a full curriculum, he was able to become fully and satisfyingly involved in school. It will be interesting to see how the increasing use of home infusion affects schooling patterns and perhaps the recommendations made by such writers as Dormandy, Gandy and Britten and Allain (28, 29).

Vocational Choices and Employment. Since Vocational Counseling is being dealt with in a special paper in this monograph, I shall refer only briefly to the pioneering work done by Katz and Husek (15, 18, 30). These writers have stressed the importance of early vocational counseling so that the individual makes appropriate schooling and vocational choices. They refer to the importance of a positive self concept as being essential in leading to a successful vocational and social adaptation.

Connor (17) and others have referred to the above-average intelligence of hemophiliacs. Weise (31) in a study in 1968 at the University of California at Los Angeles, administering a battery of psychological tests, found that 21% of his subjects were gifted-a number that far exceeds the 2% in the normal population. However, despite this there is a noticeable degree of academic backwardness which points to the need, as Connor indicates, for special educational provisions and flexibility, if possible within the context of the regular school setting.

The vocational counselor along with other center staff have a responsibility to educate state vocational rehabilitation officials and prospective employers about the facts of the disease and realistic limitations rather than allowing them to reject potential employees out of ignorance and fear. Katz (30) and Husek (18) and Spencer (16), amongst others, have addressed themselves to questions of employment. It is found in general that the higher the social class, the better the employment record. Husek (18) found that although the employment record related to clinical severity that the most significant indicator in the ability to maintain good work attendance was the successful social adaptation of the individual.

Marriage and Children. From adolescence on into young adulthood, it is extremely important for the social worker and/or the psychiatrist to help the young hemophiliac express his concerns regarding his ability to transmit hemophilia. This can have a significant influence on his self-image and his feelings about himself vis-à-vis developing social relationships. It is the experience of the Mount Sinai Hemophilia Center that this issue has been raised on many occasions by hemophiliacs in this age range. It is important to ascertain that the patient understands the facts about genetic transmission, and then if he indicates unresolved feelings about how to handle these, he needs to be helped to work through his conflicts. Studies have examined the statistics regarding marriage and sexual adjustment. Amongst these Spencer (16) found that in his group 46% had "obvious sexual or marital problems." This contrasts significantly with Husek's study (18) where a pattern of marital stability emerged and the divorce rate was less than 2%. It is recognized that these are not entirely comparable statistics since in the married group in Husek's study there may have been a number of couples who remained together but in a situation of marital and family strife. Some investigators have indicated, however, that hemophilia and the sharing of problems in the raising of the child can cement a shaky relationship. However, this in truth depends on preexisting patterns. The stress imposed by raising a hemophiliac child can produce sharply differing results which can lead to either divorce or closer family unity. By way of illustration it is this writer's experience in running a group for parents of adolescent hemophilic boys that they feel that the experience of raising a hemophiliac has brought them closer together. It is recognized however that this group is a selective one and probably represents a better adjusted group than in the general population of families with hemophilic children.

Genetic Counseling. It is timely to mention here the role of the genetic counselor. Ideally, a genetic counselor is someone with a background that includes comprehensive medical knowledge of the disease and a background in counseling. I disagree with Childs (32), who feels the ideal genetic counselor is a physician. This indeed would be the case if the physician had in addition a counseling, a social work, or psychiatric background. In general, the physician has a diverse orientation and does not have the necessary specificity to genetic and emotional implications. Childs, however, sees the only difficulty in using the physician as being the frequent reluctance of the doctor to accept the role (perhaps with good reason). Professional genetic counseling with hemophiliacs is practiced only in a few centers and more attention should be paid to this important person in the comprehensive care team. The genetic counselor should be among the first to see the family, in terms of explaining the initial facts about the disease. She or he should then be available at the request of the family and the individual at any time throughout his life but should plan, even if not so requested, to see the hemophiliac during adolescence when his initial questions about genetic transmission and his role as a father may be raised. The genetic counselor should see all family members including parents and siblings. The adjustment of the female siblings who may be carriers requires much more investigation; attention and counseling services should be directed to this area. The hemophiliac may wish again to consult with the counselor once he is dating or about to be married, and it would be valuable at that time for the genetic counselor to see the couple together so that they can learn and plan together in an atmosphere of open and frank discussion. The genetic counselor should give the facts and options regarding aminocentesis and abortion but it is not the role of the genetic counselor to make value judgments about decisions or potential decisions made by the hemophiliacs, his spouse, or his parents. This statement holds true for all members of the comprehensive care team.

Emotional Factors. Poinsard in 1956 (12) stated that the emotionally tranquil patient has less bleeding difficulty than one who is emotionally stressed. The complex relationship between stress, psychological and personality factors, and bleeding has been examined by a number of authors including Browne, Mally and Kane, and Agle and Mattsson (24, 23). It is the experience of this center, the previously mentioned authors, and among others, Bronks and Blackburn (19), that there is a positive correlation between stress and hemorrhaging. Bronks and Blackburn, however, indicate that material to date is primarily anecodotal. Agle (3) has noted that it is indeed difficult to obtain accurate statistical data, and studies to date have not been carried out with the aid of a control group.

It has been the experience of the social worker in this center that a number of patients in therapy have reported that spontaneous bleeds have occurred prior to events which have created excitement or stress in anticipation, and following periods of emotional stress and during times of depression. Agle (3) and others have observed that less hemorrhaging is reported by aggressive, outgoing well-adjusted hemophiliacs as opposed to passive, depressed, and dependent patients who bleed more frequently. He also noted that a change in the number of bleeding episodes is reported by patients who frequently switch from a passive-dependent state in preadolescence. The question of emotional stress and its effect on bleeding and capillary fragility has been reviewed by some of these authors and a positive correlation has been found in relation to ulcerative colitis (12) and hypothesized with regard to hemophilia. An examination of psychological factors, adaptive and maladaptive defense patterns, and common psychological problems will be examined in more detail in another paper in this monograph. However, it should be noted that these problems are handled by all mental health professionals on the comprehensive care team.

Home Therapy. Since the inception of home therapy a large number of hemophiliacs in this country, in Great Britain, and elsewhere have been placed on self-infusion programs. The overall advantages of home therapy were recognized immediately by all treatment personnel and in the literature. The advantages of self infusion are perhaps apparent; it allows a greater degree of autonomy for the patient and the family, cutting down on costly and time consuming visits to the emergency room of a local hospital or the treatment center, and enables the hemophiliac to miss less time in school and at work. In a study currently being undertaken by Hummel (33) for instance, early results indicate that 41% in this study note an improved attendance rate at school. However, Agle (34) and Hickman (35) have issued timely warnings about potential dangers in therapy. As the practice of home therapy rapidly increases it is important that all health care professionals responsible for recommending home therapy to a patient and his family should be aware of the disadvantages as well as the advantages. To this end each patient recommended for home therapy from this center is carefully screened by all the clinic staff, who evaluate his physical suitability and emotional readiness to handle the program. It is important that the hemophiliac and, in the case of a child, his parents be involved in understanding the details of home therapy. The social worker and other mental health professionals on the team evaluate whether the family and individual are emotionally equipped to handle this responsibility. Will they be able to judge when they need to come to the hospital and when they can handle a bleed at home? Many centers with patients on home therapy have a hot line between the hospital (usually the nurse clinician) and the family so that each transfusion done at home may be carried out with medical support. In the case of a small child, patterns of interaction between parents and child must be sufficiently stable so that they all can cope with the added dependence of the child. Patients who have a history of drug dependence (a constant threat in controlling pain in hemophilia) and of alcohol abuse, are immediately screened out. A family which has already shown signs of significant overprotection and anxiety is recommended for home therapy with caution, since the increased responsibility entrusted to the parents may cause them to make an error in judgment. Agle (34) notes that where a rejecting parent is given the responsibility of infusing the boy that he or she may withhold therapy as a punishment causing, perhaps, very severe consequences. While noting and indeed emphasizing the importance of the potential negative consequences of home therapy, it is important to be positive about this tremendous advance in the treatment of hemophilia. Those for whom home therapy is appropriate have found it a truly freeing experience both in physical and emotional terms. The author has observed, in the adolescent hemophiliacs parents' group that a number of parents and children in this group are on home infusion programs, and in one instance a 12-year-old is most successfully infusing his 6-year-old brother. This has resulted in a significant sense of pride and mastery on the part of the 12-year-old and made for a close sibling relationship. It should be emphasized that a parent must be present when the decision to transfuse a child is made and at the time when that transfusion takes place.

Treatment Modalities and Types of Intervention (see Figure 5)

There are a range of treatment modalities available to mental health professionals and the appropriate one needs to be selected. Within some modalities there are various types of intervention, which will be outlined here.

1. *Evaluation.* The evaluation session has been detailed already and this is an essential first step prior to any type of intervention that a social worker might plan.
2. *Short-term Intervention.* This is a technique frequently employed by the social worker. This may be used to deal with a particular problem or crisis or to help a family or an individual with a decision they are attempting to make. This is a brief, goal-oriented type of purposeful interaction.
   a. *Interaction in Clinic.* Where no formal, continuing contract is made with an individual or family, the modus operandi of the comprehensive care team makes it possible for brief purposeful interactions in the clinic situation. These brief interface interactions are often intense because they may take place at time of crisis. It is the experience of this center that at times of acting out or other crisis, a cathartic intervention by the social worker and other team members can be very positive.
   b. *Preparation for Surgery* Patients who are being prepared for elective surgery, increasingly being performed in this center, are evaluated by the whole team in an effort to determine not only their physical

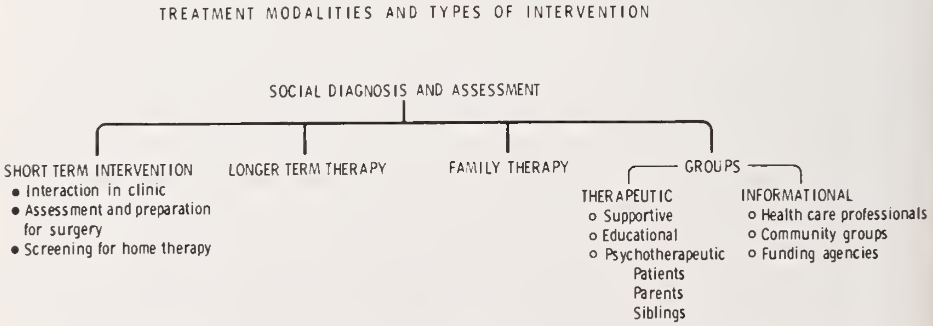
TREATMENT MODALITIES AND TYPES OF INTERVENTION
SOCIAL DIAGNOSIS AND ASSESSMENT
SHORT TERM INTERVENTION
• Interaction in clinic
• Assessment and preparation for surgery
• Screening for home therapy
LONGER TERM THERAPY
FAMILY THERAPY
GROUPS
THERAPEUTIC
o Supportive
o Educational
o Psychotherapeutic
Patients
Parents
Siblings
INFORMATIONAL
o Health care professionals
o Community groups
o Funding agencies

FIG. 5.

stability for surgery but also their ability to handle it emotionally. When necessary, elective surgery has been postponed in order to allow more time for the psychiatrist or social worker to help prepare the individual more adequately. In older patients particularly, fears that preexist the inception of factor therapy still die hard and an opportunity to ventilate these fears and concerns in a supportive atmostphere can be extremely valuable to patients in preparing them for surgery.

   c. *Screening for Home Therapy.* As mentioned previously, the social worker is involved in an evaluative interview or series of interviews with patients who are being evaluated for home therapy.

3. *Long-Term Therapy.* In a few instances longer term intervention is indicated. A contract is defined with the patient where there is a goal to work towards a specific adjustment or deal with a special problem is agreed upon. There are some situations in which a patient needs to deal in depth with his self concept not immediately specific to hemophilia before he can return to coping with the implications of the disease itself. This will take a longer period of therapy.
4. *Family Therapy.* In a chronic disease which directly affects all family members, poor adaptation on the part of the parents or hemophiliac affects the whole family. Family therapy is the preferred mode of intervention where it is felt patterns of interaction and alliances might be advantageously modified by this type of treatment.
5. *Group Therapy.* Group therapy as a successful means of intervention has been reported on by Mattsson and Agle (36), who held a series of group meetings for 10 parents of young hemophiliacs. The goal was to aid "the parents' understanding and mastery of distressing affects related to their sons' serious disorder, hence to promote the parent-child relationship." It was found that "the sharing of these common experiences and feelings brought relief to most of the parents and furthered the development of a strong group cohesiveness. Gradually the parents began to recognize their unique ways of coping with their chronic stressful situation and periods of disruptive affects." As early as 1957 Poinsard (12) recommended that "in the total management of these cases provisions should be made for the talking out of emotionally charged material for patients and parents alike, group meetings for hemophiliacs' parents, have individual therapeutic value and indirectly lead to a more tranquil parent/child relationship which is so essential to the young patient with hemophilia." These views expressed by Mattsson and Agle and Poinsard are borne out in the experience the author has had with the parents' group previously mentioned. The parents are quick to acknowledge the tremendous support derived in the sharing of common experiences. They demonstrate pride in discussing special methods of coping with problems that they are able to share with others, and the support they derive from learning that others make the "same mistakes that they do" is clear. The value of groups is increasingly

apparent for many family constellations related to the hemophiliac. Parent groups have been reported but more work needs to be done with hemophiliacs themselves and with sibling groups. Groups may be used for a variety of purposes, namely:

1. Supportive groups as mentioned.
2. Educational groups, e.g., orientation and use of health care facilities, personnel, etc., or informational groups, and can be geared to patients, families, and community groups.
3. Psychotherapeutic groups.

A group for 11–15 year old hemophiliacs being lead by two hemophiliacs in their twenties is felt to be unusual and to have a special value. It should be stressed, however, this is not a psychotherapy group and is not being run by professionals. The early indications are that the support and strength derived in mutual sharing between these adolescents who are in normal schools and do not usually meet hemophiliacs of their own age is found to be helpful and supportive. In addition the two group leaders provide positive role models for these boys. It is hoped that a report on this group will be forthcoming.

There is, therefore, a large range of therapeutic modalities available to mental health professionals in helping the hemophiliac and his family achieve a social and emotional self-direction, increased independence, and to meet particular hurdles as they arise.

The Expanded Role of the Social Worker

This paper has discussed some of the ways in which a social worker on the hemophilia care team functions. However, similar social work intervention has been found to apply to other chronic disease entities. (37). As should be clear, this goes far beyond the boundaries of traditional casework with the patient and family.

1. There is the extremely important educational role, including the education of health care professionals who are frequently uninformed and need help in expanding their horizons vis-à-vis the significance of social, emotional and environmental factors.
2. It is the obligation of the social worker to act as an informational resource for community agencies and schools, who in turn enable the hemophiliac to make a smoother transition into society. Hummel (38) and others have presented information that coincides with this center's experience that teachers are uninformed and fearful and in some instances compare hemophilia with epilepsy. As indicated previously, not only do school teachers need education, but vocational specialists, training institutions and prospective employers also need guidance and information.
3. In addition, the social worker, together with other clinic personnel, should act as a resource person and advocate for the hemophiliac and his family. This is true in the educational role mentioned above.
4. Work is done in this center to change punitive and restrictive insurance

policies; for example, Blue Cross and Blue Shield of Greater New York now cover a wider variety of services for the hemophiliac, partly as a result of efforts by the staff of this center.

5. The advocacy role which falls on all clinic members including the social worker, should also be carried more extensively into the legislative area. Comprehensive hemophilia centers contain perhaps the most accurate and up to date information on hemophilia, thus they have a special responsibility to work at a state and federal level to disseminate this information, and to support the National Hemophilia Foundation headquarters and chapter activities aimed at improving legislation.
6. Social workers may also evaluate mental health services for hemophiliacs, the strengths and gaps at a regional and national level, and work with such bodies as the Mental Health Committee of the National Hemophilia Foundation to improve services and deal with current and ongoing issues.

Despite an increase in the number of psychosocial studies, a comprehensive review of the literature reveals that very few have dealt with the overall question of social adaptation, Goldy and Katz (10) being a notable exception.

However, this author feels there is a need for continuing research, particularly in view of the changes precipitated by the improvement in concentrate therapy and the increase in home therapy. There will be changes in psychosocial functioning which should be evaluated with a view to shifting mental health services to meet newly defined needs. The study techniques used in this center lead to the formulation of research needs, and an initial data base is made during the treatment process for such research. Although little work has been done to date on how the hemophiliac views himself; research has currently been undertaken by Markova (39) in this area. Finally the effect on female siblings, their role as carriers, and ways of working with them, merit further investigation.

References Cited

1. Katz, A. H.: Psycho-Social Problems in Hemophilia, Social Casework, June 1959.
2. Agle, D. P. and Mattsson, A.: Emotional Health in Hemophilia, National Hemophilia Foundation (Pamphlet).
3. Agle, D. P.: Psychiatric Studies of Patients with Hemophilia and Related States, Arch Int Med 114:77-82, 1964.
4. Boon, R. A. and Roberts, D. F.: The Social Impact of Hemophilia, Biosoc Sci 2:237-63, July 1970.
5. Frommer, E. and Ingram, G. I. C.: Haemophiliacs and Their Doctors, the Value of Haemophilia Centres, Practitioner 202:413-420, March 1969.
6. Hurt, C. H.: Psychological and Social Aspects. In *Comprehensive Management of Hemophiliacs*. Edited by D. C. Boone. 1975 (In Press).
7. Brinkhous, K. M.: Changing Prospects for Children with Hemophilia, Children 17:222-227, November-December 1970.
8. Petit, C. R. and Klein, G. H.: Hemophilia, Hemophiliacs, and the Health Care Delivery System. DHEW Publ. No. NIH 76-871.
9. Hurt, C.: Psychiatric Social Work Program in Hemophilia, *A Total Approach To Treatment and Rehabilitation*. Orthopedic Hospital, Los Angeles, August 1968.
10. Goldy, F. B. and Katz, A. H.: Social Adaptation in Hemophilia, School of Public Health University of California at Los Angeles, (Reproduced by the National Hemophilia Foundation), Children 10:189-193, 1963.

11. Myers, R. D.: The Social and Economic Impact of Hemophilia – A survey of 70 cases in Vermont and New Hampshire, Am J Pub Health 62:530–535, 1972.
12. Poinsard, P. J.: Psychiatric Aspects of Hemophilia. In *Hemophilia and Hemophiliod Diseases*. Edited by K. M. Brinkhous, University of North Carolina Press, Chapel Hill N.C. 1957, p. 249.
13. Agle, D. P. and Mattsson, A.: Psychiatric Factors in Hemophilia, Methods of Parental Adaptation. Edited by R. Gourdeau. Biblioteca Hemotologica 34:89–97, 1970.
14. Mattsson, A. and Gross, S.: Adaptational and Defensive Behavior in Young Hemophiliacs and Their Parents, Am J Psychiat 122:1349, 1966.
15. Katz, A. H.: Vocational Problems in Hemophilia, Ann NY Acad Sci 240:221–225, 1975.
16. Spencer, R. F.: Incidence of Social and Psychiatric Problems in a Group of Hemophilic Patients, N Carolina Med 29:232, 1968.
17. Connor, F. P.: The Hemophilic Child in School, Ann NY Acad Sci 240:238–245, 1975.
18. Husek, J. M.: Social Aspects of Hemophilia. School of Public Health, University of California at Los Angeles, October 1964.
19. Bronks, I. G. and Blackburn, E. K.: A Socio-Medical Study of Hemophilia and Related States, Brit J Prev Med 22:68–72, 1968.
20. Lockyer, Forbes, C. D. and Markova, I.: Hemophilia, Some Facts and Problems for Social Work. Unpublished Paper.
21. Favre-Gilly, J.: Medical Social Aspects of Hemophilia, Edited by K. M. Brinkhous. *Hemophilia and Hemophiliac Diseases*. North Carolina Press, Chapel Hill, N.C. 1964, pp. 385–389.
22. Agle, D. P.: Psychiatric Complications of Hemophilia, (Edited by Brinkhous, K.) In *The Hemophilias*. University of North Carolina Press, Chapel Hill, N.C., 1964, pp. 359–362.
23. Alby, J. M., Alby, N. and Caen, J.: Problems Psychologiques de L'hemophile, Rev Franc Hemat 2:119, 1962.
24. Browne, W. J., Mally, M. A., Cane, B. P.: Psycho-Social Aspects of Hemophilia: A Study of 28 Hemophiliac Children and their Families, Am J Orthopsychiat 30:730, 1960.
25. Jones, P.: *Living with Haemophilia*, F. A. Davis, 1974.
26. The Hemophiliac Child in School. Pamphlet published by the National Hemophilia Foundation. 1975.
27. Ciriello-Mould, P., pamphlet on the Hemophiliac in School. 1975.
28. Dormandy, K. M., Gandy, R. H. and Britten, M. I.: Problems of Management of Children with Coagulation Disorders, *Current Studies in Hemophilia*. Proceedings from the 3rd annual Congress of World Federation of Hemophilia, Paris 1965. Biblioteca Hematologica 26:171–175 N.Y., Karger, Basel 1966.
29. Allain, J. P.: A Boarding School for Hemophiliacs: A Model for Comprehensive Care of Hemophilic Children. Ann NY Acad Sci 240:226–237.
30. Katz, A. H.: *Hemophilia, a Study in Hope and Reality*. Charles C Thomas: Springfield, Illinois, 1970.
31. Weise, P.: Psychological Programs in Hemophilia. A Total Approach to Treatment and Rehabilitation, Orthopedic Hospital, Los Angeles, August 1968.
32. Childs, B.: Approaches to Genetic Counseling, Ann NY Acad Sci 240:132–137, 1975.
33. Hummel, L.: Research Study in Progress regarding the Emotional Implications of Home Care on Emotional Adjustment and Schooling.
34. Agle, D. P.: Psychological factors in Hemophilia – The Concept of Self-Care, Ann NY Acad Sci 240:221–225, 1975.
35. Hickman, F., Discussion paper: Disadvantages of Home Treatment, Ann NY Acad Sci 240:255–256, 1975.
36. Mattsson, A. and Agle, D. P.: Group Therapy with Parents of Hemophiliacs. Therapeutic Process and Observations of Parental Adaptations to Chronic Illness in Children, J Amer Acad Child Psychiat 113:558–571, 1972.
37. Regensburg, J.: A Contribution from the Practice of Social Work to Education for the Health Professions July 1975. Unpublished Manuscipt.
38. Hummel, L.: Personal communication.
39. Markova, I.: Personal communication.

Selected General Bibliography

1. *British Medical Journal*—Leading article—Life as a Haemophiliac September 1968.
2. Bruhn, J. G., Hampton, J. W. and Philips, B. M., A Psycho-Social Study of Married Hemophiliacs and Their Wives and Hemophiliac Adolescents and Their Parents. *J. Psychosom Research* 15:293–303 September 1971.
3. Burke, C., Working with Parents of Children with Hemophilia, *Nursing Clinics of North America*. 7:787–798 December 1972.
4. Caldwell, H. S., Leveque, K. L., Lane, D. M. Group Psychotherapy in Management of Hemophilia. *Psychol. Rep.* 35 (11):339–342 August 1974.
5. Childs, B., Approaches to Genetic Counseling, *Annals of the New York Academy of Sciences* 240:132–137 1975.
6. Dowling, J. P., Preventing Dependency Patterns in Chronically Ill Children. *Social Casework* 16:395–40 1960.
7. Garlinghouse, J. and Sharp, L. J., The Hemophiliac Child Self-Concept and Family Stress in Relation to Bleeding Episodes. *Nursing Research* 17:32 1968.
8. Grunfeld, B., Some Psychosocial Aspects of Hemophilia, A Population Study. *Acta. Sociomed. Scand.* 2 (2):103–107 1970.
9. Hirschman, R. J. and Libby, E. E., Editorial Notes. Personal Burdens in Hemophilia. *Annals of Internal Medicine* 77:4 651–652 October 1972.
10. Ikkala, E., Haemophilia, a Study of its laboratory, clinical and genetic and social aspects based on known Haemophiliacs in Finland, *Scand. J. Lab. Invest* Suppl: 45 V. 12. 1960.
11. Katz, A. H., Psycho-Social Problems In Hemophilia. *Social Casework* June 1959.
12. Katz, A. H., Social Adaptation in Chronic Illness. A Study of Hemophilia. *American Journal of Public Health*, 53:1666–1675 1963.
13. Malikin, D., Hemophilia: Psycho-Social Aspects. *Journal of Rehabilitation* 37 (3):36–38. May–June 1971.
14. Massie, R. and Massie, S., Journey. A. A. Knopf 1975.
15. Mattsson, A. and Gross, S., Social and Behavioral Studies of Hemophilic Children and Their Families: *Pediatrics* 68:952–962 1966.
16. Miller, J., Haemophilia, A Challenge to Social Work. *Social Work Today* 4:16 501–504 1973.
17. National Hemophilia Foundation Booklet, Home Therapy for Hemophilia, A Physician's Manual. Medical and Scientific Advisory Council of the National Hemophilia Foundation. June 1974.
18. Olch, D., Effects of Hemophilia upon Intellectual Growth and Academic Achievement. *Journal of Genetic Psychology*. 119:63–74 1971.
19. Olch, D., Personality Characteristics of Hemophiliacs: *Journal of Personality Assessment* 35 (1) 72–79. February 1971.
20. Patterson, P. C., Hemophilia—The New Look. *Nursing Clinics of North America*. 7: 777–785 December 1972.
21. Poinsard, P. J., Psychiatric Aspects of Hemophilia. Editor, Russlem, H. *Proceedings of the Institute on Hemophilia*. (Oct. 22–23, 1964.)
22. Salk, L., Hilgartner, M. and Granich, B., The Psycho-Social Impact of Hemophilia on the Patient and his Family, *Social Science and Medicine* 6:491–505 1972.
23. Spencer, R. F., Psychiatric Impairment Versus Adjustment in Hemophilia: Review and Five Case Studies. *Psychiatry and Medicine* 2:1–12 1971.
24. Taylor, C., Educational Vocational Programs in Hemophilia. A Total Approach to Treatment and Rehabilitation. Orthopedic Hospital, Los Angeles. August 1968.
25. Weise, P., Psychological programs in Hemophilia. A total approach to treatment and rehabilitation Orthopedic Hospital, Los Angeles, August 1968.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol 44, No. 3, May-June, 1977
Printed in U.S.A.

Psychiatric Aspects of Hemophilia

DAVID L. JONAS, M.D.

Hemophilia is a chronic disease. The psychiatrist, as a member of a multidisciplinary treatment team, has opportunities for active intervention in preventing or correcting maladaptive behavior at all levels of the hemophiliac's emotional development. These interventions may involve the individual patient, other family members, other medical staff, and those involved in the patient's educational process.

Childhood

The concept of genetic transmission is central to an understanding of developmental interactions between the hemophiliac and his family. Most cases have a documented genetic transmission through the mother. The predictably resulting maternal guilt about transmitting this chronic disease to her child is well documented (1–4), and the mother's ability or inability to master this guilt is decisive in influencing the hemophiliac's lifelong emotional development (4–7). It may be noted that patterns of parent-child interactions are similar in families where there is and families where there is not a definitely documented history of maternal familial transmission (2, 8, 9). One may postulate that maternal guilt operates in the latter case because of the conscious or unconscious thought that there may be an undetected genetic transmitter in the maternal line.

The sequelae of guilt are omnipresent. Infrequently, the mother or both parents may desert or otherwise overtly reject the child (2). More subtly, the illness may be intermittently denied by the parents, with consequent inadequate medical treatment of the child. The much more common pattern, however, is extreme anxiety and overprotectiveness by the mother (2, 4, 6, 8, 10). The hemophilic child is then likely to become overdependent, clinging, and isolated, with consequent impaired ability to form healthy object relations in later childhood and adulthood (11). The value of psychotherapeutic intervention to influence the quality of the parent-child relationship is evident. The child himself is frequently depressed and abnormally fearful. His fears are based on his parent's expectations about the future course of his illness and also on his personal experience with bleeding episodes. The child fears the pain of bleeding itself, but sometimes he is even more fearful of subsequent immobilization and enforced inactivity (6). Expression of normal aggressive drives may be hampered (4, 12, 10) by fear of injury or fear of being reprimanded by the overprotective parent, with subsequent utilization of less

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From the Department of Psychiatry, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Requests for reprints should be sent to: David L. Jonas, M.D., Department of Psychiatry, The Mount Sinai Hospital, Fifth Avenue and 100 Street, New York, N.Y. 10029.

desirable defenses such as excessive denial, counterphobic behavior, or regression to infantile levels of passivity (6, 9). Psychotherapeutic intervention at such times is of value in permitting the child to ventilate fears and aggressive feelings. The therapist can utilize the child's developing intellectual capacities to reeducate him (and his parents) about contemporary concepts of care, including the value of appropriate physical exercise and aggressive play.

The psychiatrist, with other members of the treatment team, must be a forceful advocate of as normal an educational process as possible for the hemophilic child (4). Home tutoring programs, if not indicated for severe medical disability, are undesirable. Lack of normal peer contact predisposes to later development of permanent defects in object relations. Likewise, special classes or special schools are usually undesirable. Much reeducation may be necessary in dealing with the fears and misconceptions of parents and educators about the hemophiliac's school requirements.

The interactions of the hemophilic child with his affected or unaffected siblings merit consideration. Heightened identification with hemophilic siblings has been observed, with intense protective feelings and "qualities of twins within a sibship" (13). Older affected siblings may be utilized therapeutically as objects for positive identification by the younger child as the older brother develops physical and social skills (6). The older sibling may assume an active guiding role in the younger child's development, with consequent increase in his own self-esteem and sense of independence. We know of one such relationship in which the older brother takes much responsibility for the younger brother's home factor infusions. Unaffected siblings may resent the extra attentions that their affected siblings receive, with notably distorted sibling rivalry as a result. Unaffected siblings may utilize maladaptive behavior to gain extra attention. Appropriate therapeutic intervention with the entire family is often helpful in such situations.

The hemophiliac's first surgical experience may occur during childhood (14). The quality of his pre- and postoperative adjustment is affected by parental attitudes (i.e., their degree of protectiveness and anxiety and the child's consequent degree of dependence and fear). Realistic and unrealistic fears of bleeding, pain, and immobilization must be dealt with prophylactically to avoid maladaptive regression pre- and postoperatively.

Work with parents of the hemophilic child is particularly important to help them understand their feelings and minimize the previously mentioned overprotective, anxious, guilt-determined behavior. Mothers are frequently depressed (2, 6, 9, 12) and this may be influenced by prior exposure to deaths of affected relatives. The father may harbor latent resentment towards his wife for transmitting the disease into his family, or toward his son for monopolizing the wife's attentions. Fathers may tend to isolate themselves from the close mother-son pair. The father is needed by the hemophilic boy as a healthy role model and as an object of masculine identification to resolve conflicts over the ambivalent mother-son relationship (4, 5, 8, 15) and therapeutic efforts should be directed toward making him as active a participant in his son's treatment program and family life as possible. Also, one must encourage the maintenance of the normal mother-father alliance to provide appropriate parental structure in the child's development. Mothers' groups and groups for both parents have helped parents to understand and master their own feelings (1, 7). Such groups have allowed parents to share predictable feelings of isolation, fear, guilt, and anger, as well as to establish positive identification within the groups. Recognition of parents' affective responses and adaptive or maladaptive psychological defenses promote more appropriate child-rearing (16).

Young Adults

As the hemophiliac matures, one may note the development of a normal spectrum of psychopathology. It is not clear if there is an increased prevalence of overt psychopathology in adult hemophiliacs. Previous studies suggest a normal prevalence of overt psychiatric disturbance in these adults (6, 17, 18) and our Mount Sinai Hemophilia Clinic experience tends to confirm this. However, since our clinic population probably represents a better adjusted group, we might speculate that a larger number of maladapted people are not in active clinic contact. Likewise, previous observations that there may be a "low incidence of symptoms considered disturbing to the patients themselves" except at times of "acute decompensation" (13) suggest that many maladapted patients do not call themselves to our attention.

Symptoms of depression are common in this young adult group (19, 18) and exploration of depressive ideation often yields distorted, overly pessimistic expectations about the disease and potential future disability. Depressive symptoms also surface when the close mother-son relationship previously alluded to is threatened or broken by the changing demands of adult life. Appropriate psychotherapeutic support is helpful during such periods, with particular emphasis on realistic perception of physical limitations, coping with changing family interactions, and changing social and sexual roles. Intervention with one or both parents may ease the patient's separation difficulties (as well as theirs). In addition, antidepressant and/or antianxiety medications, as clinically indicated, are helpful.

Character disorders are notable among adult hemophiliacs. The occurrence of a passive-dependent personality disorder has been linked to prior maternal overprotective behavior, with a resulting retiring, irritable, and depressed adult who assumes few realistic adult responsibilities (4, 9, 10). This type of patient is particularly prone to drug abuse in his efforts to avoid confrontation with normally stressful daily events.

Distorted patterns of physical activity may take several forms and are again usually associated with childhood overprotectedness. The distortion may take the form of excessive physical withdrawal and the adaptation of the previously described passive-dependent state. It may also take the form of excessive risk-taking behavior (2, 6, 10) in which denial and counterphobic defenses produce participation in foolish, "daredevil" activities involving excessive exposure to physical danger.

Sexual difficulties, including impotence and premature ejaculation, are notable in our adult clinic population. This supports prior reports of increased frequencies of sexual and marital problems and ambivalence towards females, related to prior distortions of mother-son relationships (1, 19, 22). As previously reported, ambivalent identification with the mother can produce sadomasochistic feelings or behavior towards women, avoidance of women, or "seeming interchangeability of women" where they are "regarded as need-fulfilling objects" (13). In addition, our observations confirm that an adequate male sexual identification is favored by adequate association with other male peers during childhood and adolescense. The psychiatrist may be useful in augmenting the genetic counselor when the adult hemophiliac considers a potential parent role, since the patient's anticipated experience as a parent will be influenced by the quality of his child-parent interactions. Similarly, female carriers' roles as potential mothers of hemophiliacs are tied to their own mothers' adaptations to affected sons.

Drug abuse, including alcohol abuse, may serve a variety of purposes for the hemophiliac (19, 20). We have noted the use of sedating and analgesic medications for self-treatment of depression in adolescent and young adult hemophiliacs; hypnotics and analgesics may be inappropriately used for self-treatment of anxiety. In addition, we have observed the abuse of alcohol and analgesics for attempted self-treatment of frank psychotic symptoms as well as severe anxiety in several schizophrenic hemophiliacs.

It has been previously noted that adequate education of other medical staff about the realistic requirements for pain medications during the hemophiliac's emergency room and other hospital contacts is an important factor in the prevention of later drug abuse (21). Standard psychiatric medications, including antidepressants and antipsychotics, need not be significantly altered with respect to the hemophiliac's coagulopathy, but potentiation of sedation from these medications by analgesics should be kept in mind.

A relationship between bleeding episodes and emotional stress has been frequently reported (1, 3, 9, 10, 12). Our experience has confirmed these observations; conflicts with other family members, anticipation of distasteful tasks, suppression of hostile thoughts and impulses, and thwarted sexual advances have directly preceded frank bleeding episodes in our patients in the absence of notable trauma. Prior studies have reported a decreasing frequency of bleeding episodes associated with personality change from a passive to a more aggressive, independent state (6, 9, 10). One might thus speculate that effective psychotherapeutic intervention might have a beneficial effect on long-term frequency or severity of bleeds and incapacity; controlled, non-anecdotal data to support this speculation is presently unavailable.

The physical, psychological and economic advantages of homecare for hemophiliacs are well documented, and our clinic advocates this treatment modality when applicable (23). Such a program should include adequate psychiatric participation. Our Mount Sinai protocol includes psychiatric assessment as part of initial home-care screening and as part of continuing home-care follow-up. Initial screening includes assessment of the patient and his family, their realistic and unrealistic expectations, and their intelligence and realistic acceptance of his illness. Gross defects in reality testing, alcohol or other drug abuse, overt sociopathy, and unstable living situations bode poorly for therapeutic success. Defects in judgment or excessive utilization of denial may lead to under- or overtreatment of bleeding episodes, with resulting excessive bleeding complications at the one extreme and excessive transfusion morbidity at the other. Once home-care is started, periodic multidisciplinary monitoring includes psychiatric assessment, with particular focus on emotional reactions to self-treatment, effects on family structure, adequacy of therapeutic judgement, and patterns of treatment (factor and/or ancillary medications).

Older Adults

Psychiatric intervention with older hemophiliacs presently involves a good deal of reeducation. Although there are few aged hemophiliacs today (5), we will be dealing with a larger number of older adult patients as contemporary medical techniques prolong the hemophilic life span. A study of personality factors in hemophiliacs, using control-group design, found that increasing physical handicap corresponds to increasing "psychosomatic disorders," shyness, and depression, and to decreasing masculinity and sociability (18). Thus the older, more disabled hemophiliac may be more prone to emotional maladaptation. Having been treated before the era of specific factor replacement, and sometimes before any replacement therapy at all, many older patients are extremely fearful of any medical intervention, based on their past experiences with inadequate hematologic and orthopedic management, extensive pain, and intermittently, death of affected peers from bleeding complications (8).

The normal aging process carries with it a likelihood of hospitalization for a variety of nonbleeding, age-related medical and surgical disorders. This is a particularly difficult time for the older patient whose prior bleeding-related hospitalizations have been so frightening. Once the initial resistance to entering the hospital is overcome, one often encounters extreme regression in the face of this stress, manifested by childlike, passive, helpless behavior, belligerence, and excessive difficulties with hospital routine. The psychiatrist's role in dealing with these fears and predictable regressions becomes a key to successful hospital management, including rehabilitation programs.

Surgery is a particular intrahospital stress; our extensive surgical experience at The Mount Sinai Hospital has established the value of pre- and postoperative psychiatric support for successful surgical management. Routine preoperative psychiatric interviews focus on the patient's particular fears regarding hemostasis, pain, immobilization, and functional expectations. Past psychiatric history is reviewed. Past hospital and surgical experiences are reviewed. Potential for postoperative depression, psychosis, or other excessive regression is assessed. Elective surgery for more disturbed patients is, if possible, scheduled at emotionally optimal times.

Postoperatively, dependency conflicts predominate (predictably, in view of the aforementioned early life dependency conflicts inherent in many hemophilic mother-son systems). Conflicts about analgesic and factor requirements are often variations on such dependency themes. Overt dependence and passivity may predominate in the postoperative course, making mobilization and participation in physical therapy programs contested issues. Alternately, the conflict may be expressed as pseudo-independence, with difficulties in patient-staff or patient-patient relations as presenting issues. Appropriate interpretations, clarifications of issues, and resolute support to staff and patients is essential to optimal postoperative rehabilitation. The psychiatrist is useful at such times to educate the floor staff about hemophilia and its particular emotional sequelae, often to correct their distortions about the disease and its proper hospital management.

Summary

Hemophilia, as a chronic disease, challenges the full adaptational capabilities of the patient and his family through all stages of development. Adequate early and lifelong psychiatric intervention, as indicated, may help the hemophiliac achieve maximal adaptation; this has been aptly described by Agle (referring to Poinsard) as "overcoming overdependence, avoiding excessive revolt, and considering the limitations of his illness as a challenge to be accepted" (4).

References

1. Poinsard, P. J.: Psychiatric Aspects of Hemophilia. In *Hemophilia and Hemophilioid Diseases*. Edited by K. M. Brinkhous. University of North Carolina Press, Chapel Hill, N.C., 1957, p. 249.
2. Alby, J. M., Alby, N., and Caen, J.: Problemes Psychologiques de L'Hemophile, Nouv Rev Fran Hemat 2:119, 1962.
3. Poinsard, P. J.: Psychiatric Aspects of Hemophilia. In *Proc of Institute for Hemophilia*. Edited by Russalem 1964–1965.
4. Agle, D. and Mattson, A.: Psychiatric and Social Care of Patients with Hereditary Hemorrhagic Disease, Mod Treatment 5:111, 1968.
5. Katz, A. H.: Social Adaptation In Chronic Illness: A Study of Hemophilia, Am J Pub Hlth. 53:1666, 1963.
6. Mattson, A. and Gross, S.: Adaptational and Defensive Behavior in Young Hemophiliacs and Their Parents, Am J Psych 122:1349, 1966.
7. Agle, D. P. and Mattson, A.: Psychiatric Factors in Hemophilia Methods of Parental Adaptation, Bibl Haemat 34:89, 1970.
8. Goldy, F. B. and Katz, A. H.: Social Adaptation in Hemophilia, Children 10:189, 1963.
9. Mattson, A. and Gross, S.: Social and Behavioral Studies on Hemophiliac Children and Their Families J Ped 68:952, 1966.
10. Agle, D.: Psychiatric Studies of Patients with Hemophilia and Related States, Arch Int Med 114:76, 1964.
11. Green, M. and Solnit, A. J.: Reactions to the Threatened Loss of a Child: A Vulnerable Child Syndrome, Pediatrics 34:58, 1964.
12. Browne, W. J., Mally, M. A. and Kane, R. P.: Psychosocial Aspects of Hemophilia: A Study of Twenty-Eight Hemophilic Children and Their Families, Am J Orthopsych 30:730, 1960.
13. Spencer, R. F.: Psychiatric Impairment Versus Adjustment in Hemophilia: Review and Five Case Studies, Psych Med 2:1, 1971.
14. Gilbert, M.: Reconstructive Surgery. This volume.

15. Spencer, R. F. and Behar, L.: Adaptation in Hemophilic Adolescents. Psychosom 10:304, 1969.
16. Mattson, A. and Agle, D. P.: Group Therapy with Parents of Hemophiliacs, J Am Acad Child Psych 11:558, 1972.
17. Bronks, I. G. and Blackburn, E. K.: A Socio-Medical Study of Haemophilia and Related States, Brit J Prev Soc Med 22:68, 1968.
18. Steinhausen, H. C. A Psycho-Clinical Investigation in Adult Hemophiliacs, Jnl of Psychosom Res 19:295, 1975.
19. Spencer, R. F.: Incidence of Social and Psychiatric Problems in a Group of Hemophiliac Patients, NC Med J 29:332, 1968.
20. Alby, N.: Aspects Psychologiques de L'Hemophilie, Bibl Haemat 34:83, 1970.
21. Frommer, E. and Ingram, G. I. C.: Haemophiliacs and Their Doctors, Practitioner 202:413, 1969.
22. Bruhn, J. G., Hampton, J. W., and Philips, B. U.: A Psycho-Social Study of Married Hemophiliacs and Their Wives and Hemophiliac Adolescents and Their Parents, J Psychosom Res 15:293, 1971.
23. Levine, P. H.: Efficacy of Self-Therapy in Hemophilia, New Engl J Med 291:1381, 1974.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May–June, 1977
Printed in U.S.A.

Vocational Rehabilitation and the Hemophiliac

FREDERICK N. MARSHALL, M.A.

Many professionals and nonprofessionals view hemophilia as the "bleeders disease" and thus create an overprotective attitude, severely limiting educational and vocational opportunities for the hemophilic patient. They feel that hemophiliacs should and must be directed towards less physically demanding activities. An example of such an attitude is seen in the following statement by Pierre Isarn:

> "Generally speaking, the hemophiliac must not be exposed to falls, trauma, or superficial wounds. Strenuous efforts are forbidden to him owing to the weakness of his musculature. For this reason all professions dealing with wood, metals, and construction, as well as the occupation of farmer or agriculture worker, are to be avoided. Because of hemarthrosis in the knees, all the occupations which necessitate moving about a great deal or prolonged standing such as store clerk or hairdresser are excluded. A sedentary occupation, carrying a large number of hours of work sitting down, is recommended. The wage-earning jobs will be preferable to independent professions. Professional training can be acquired by correspondence courses, in a secondary technical school, in a medically supervised vocational boarding school for hemophiliacs, or in a professional readaptation center for adults. The problems set by the employment of the hemophiliac and his integration in the workaday world are then discussed (1).
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> Margaret Britten, an educational researcher reported:
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> In treating these patients, two essential features are always in evidence. One is that potential crippling lesions should receive immediate and adequate treatment; the second is that unless these children are educationally equipped to hold sedentary jobs their future employment will be precarious. They miss much school time and often receive a very inadequate preparation for life. Over the years it has become clear to us that these difficulties could be solved only by the provision of a special boarding school for severely affected hemophilic boys, and that the boarding school should be run in close association with a hemophiliac treatment center. It is not enough for young hemophiliacs merely to survive, nor even for them to grow to manhood with good physique, they must also be able to take their place in society as well-integrated, independent individuals, able to earn a salary and support their families. Since all forms of manual labor are closed to adult hemophiliacs, educational attainments achieved during childhood are obviously of the greatest importance. Success is possible only if their education has fitted them for clerical, professional or other work which does not involve physical strain. Constant interruptions in their schooling will

From the Department of Rehabilitation Medicine, The Mount Sinai Hospital, New York, N. Y. 10029.

bar them from just this type of work and livelihood. Because the illness is utterly unpredictable in its periodicty and because minor injuries are inseparable from normal childhood, good and continuous education can be achieved only if school and treatment centers work together as an integrated unit" (2).

The above concepts have been repeated frequently: "Hemophiliacs should and must be protected from "physical strain." "They should be placed in a structured environment so that those suffering from the "Royal Disease" can more adequately be cared for." "When the hemophiliac is released from institutional care, make sure he is selectively employed in sedentary, structured, protective jobs."

We would like to help put to rest the existing myth that hemophiliacs should be isolated from the mainstream of society for their own protection. Lois Dowson Bedard states: "The hemophiliac is first a person, and secondly a person with hemophilia. Although hemophilia cannot be cured, it can be so minimized as a health disability that the life expectancy and life style of the hemophiliac born in the 70's is that of his peers. Early appropriate, aggressive treatment will normalize the life and living of the hemophiliac" (3). Taylor says, and we wholeheartedly agree, that "Hemophiliacs have found work that is both safe and satisfying in all job categories" (4). Alfred Katz reports, "Hemophiliacs are by no means confined to sedentary occupations. Many are working at such occupations as longshoremen, housepainters, construction workers, waiters, delivery boys and gas station attendants" (5).

The vocational rehabilitation counselor accepts referrals from the comprehensive care team, meeting with members on a regular weekly basis. The counselor's services are directed towards helping the client select the appropriate educational and occupational goal through interviews, testing, and counseling; few restrictions should be placed on the hemophiliac's occupational choices.

The counselor at our hemophilia clinic is fortunate in that patients can be offered, on an as needed basis, an additional service called a diagnostic work evaluation. This diagnostic evaluation is the first step in a process and is effected through the use of work sample techniques and psychometric instruments appropriate to the client's needs and capacity. This is determined by the client, counselor and the vocational evaluator. The program serves a three fold function:

1. To help determine whether the client is capable of vocational training.
2. To determine the client's specific strengths and weaknesses, his work habits and skills.
3. To determine the client's potential and suitability for training and the manner in which the individual situation may be best served.
4. To assess the client's psychosocial make-up in a work-oriented atmosphere.

Following the diagnostic evaluation there can be a period of work experience called a personal adjustment training program. The work experience is provided in a sheltered environment where the patient is taught skills and good work habits in a warm work-oriented atmosphere. The client learns to increase his tolerance and develop good interpersonal relationship patterns. The length of stay within this facility can vary with the individual needs of the client. Information is then presented to the client through individual or group counseling sessions so that the client can hopefully accept a realistic educational, vocational training or job-oriented goal.

Most hemophilic clients, however, go through an initial interview, counseling and referral without the diagnostic evaluation. The following case histories illustrate how the vocational rehabilitation counselor functions within the comprehensive care team

Case Report

F. R. became conscious of his hemophilia condition at the age of eight. He was unable to walk, had frequent bleeding episodes and was forced to leave school. The youngster occupied his time by becoming proficient in painting, carpentry and stamp collection. In 1972, F. R. came to New York City, from Cuba, along with his parents and three siblings. F. R.'s family is a warm, cooperative family with each member exhibiting concern for other family members.

F. R. appeared at the Mount Sinai Hemophilia Clinic with severe muscle contractures and bleeding problems. An additional handicap was his inability to speak or understand English. After caring for the young man's medical problems, he was referred to the rehabilitation counselor in the Department of Rehabilitation Medicine.

During the counseling sessions, and utilizing an English-speaking Spanish employee, it was decided to administer the Weschsler Adult Intelligence Scale (W.A.I.S.), Wide Arrange Achievement Test (W.A.A.T.), and the Kuder Preference Inventory.

Results on these tests indicated that F. R. was functioning in the bright-normal range of intelligence and at an eleventh grade school level. He exhibited high interest in the social service area along with the engineering field. It was decided to enroll F. R. in an accredited English remedial course in order to improve his English skills and to place the young man in the hospital's prevocational evaluation unit where his eye-hand coordination, finger dexterity, physical and emotional tolerance, and overall abilities could be measured. F. R. showed an intense interest in manual skills and design, had excellent finger dexterity, and talked of becoming a draftsman. He spent the next few months in the sheltered workshop learning good work skills and habits, to overcome his shyness in speaking English, and to develop self-confidence. Trained in the workshop in the use of the pantograph machine, F. R. was able to earn a good hourly rate of pay because of the high quality of his work. With the use of the machine, F. R. manufactured signs, name plates, plaques and bracelets. The young man constantly spoke of architectural design. An appropriate school was found by the Office of Vocational Rehabilitation and F. R. was placed there for a period of one year. In less than two years from the time of his initial referral to the clinic, F. R. had "made it." Soon after school graduation, F. R. was using sharp instruments and lifting heavy materials and had been hired by a respectable firm as an architectural design draftsman.

L. M. is a 23-year-old hemophilic man, presently attending a well-regarded university as an art major. He was born in New Jersey, the only child of professional parents. He always seemed to be at odds with his father and mother, who he felt resented him because of his disability. This family problem contributed towards L. M.'s pattern of overextending himself in relationships with peers and adults. The resultant behavior often ended in physical fights with teachers, friends, and strangers. L. M. would try to prove he could drink more, fight harder, run faster, and leap higher than anyone else.

Five years ago, the young man reported to the clinic with contractures and recurrent severe knee bleeding episodes. The medical problems were alleviated and the counselor worked with the young man, concentrating on his negative behavior. With difficulty, L. M. graduated from high school and expressed an interest in metal sculpture. Vocational, intelligence and interest tests were administered and indicated that he had chosen the appropriate field. L. M. wanted to attend a well-known northeastern art college. On hearing that the young man was a hemophiliac and of his desire to become a metal sculptor, the school officials refused to consider his plans. The rehabilitation counselor, with the help of the doctors, educated the officials as to blood replacement therapy, home care, and other information about hemophilia. The officials relented, allowing L. M. to participate in the coursework of his choice. L. M. is presently in his senior year at college and works on 30-foot-high metal sculptures. Minor incidents of bleeding have not deterred him or interfered with his work.

A. V. is a 30-year-old man of Spanish extraction. He was born and reared in New York City, one of seven children. His parents separated when the client was 12 years old. A. V. became a heavy drinker, graduating to hard drugs in a few years. He is single and has a child by a severely retarded woman. His child has been in and out of homes for emotionally disturbed children for the past eight years. A. V. reported to the hemophilia clinic in 1969 because of bleeding caused by dental problems. He was hospitalized, his dental and medical problems were attended to and he was then referred to the clinic's vocational rehabilitation counselor. During the counseling sessions, it came to light that A. V. was a patient in a methadone clinic and that he had attended that clinic on a regular basis for several months. We were told that he would be allowed to take his methadone at home and that he could look forward to being terminated from the drug program in the next few months.

With the help of the public school authorities, the client and the counselor set up an educational program in order for A. V. to obtain his high school equivalency diploma. A. V. then applied for and got a job as a clerk in a dry goods establishment. This was in 1970. Since that time he has become one of the firm's best salesmen and has been drug free for the past five years.

L. B. is a 23-year-old man, living in upstate New York and presently attending a university. He lives with his parents and a brother. L. B.'s family is a very warm, closely knit group and they have shown sincere concern about his health and welfare. L. B. came to Mount Sinai Hospital's hemophilia clinic in 1969 with bleeding in the elbow, knee and ankle joints. He suffered from severe muscle contractures and had been braced and confined to a wheelchair since the age of eight. Doctors set up a program to stretch the youngster's joints with the use of plaster casts. After a period of time, the vocational rehabilitation counselor was involved in helping him plan his future.

L. B. was well liked in school. He had been elected class president several times and also had given public speeches. Test results on the W.A.I.S. indicated that L. B. was functioning in the above-average intellectual range with a full scale I.Q. of 113, a verbal scale of 131, and a performance scale of 89. His parents were overprotective, which L. B. resented and reacted to with hostility and anger. The counselor visited them in their home in upstate New York in order to get them to cooperate with their son's rehabilitation program. They agreed to encourage L. B. to be more independent. L. B. compensated for his physical impairment by often fantasizing that he'd like to be a football player, basketball player or a track star. Not being able to accomplish these goals he became obsessed with meeting professional athletes. Counseling helped the youngster to become more reality oriented. He finally decided on a career in communications. His medical needs are cared for by a local hospital and he has received a license to operate a motor vehicle, a license that had been denied him previously by the Motor Vehicle Bureau because of his hemophilia.

F. B., a 21-year-old man came to the hemophilia clinic in 1969, suffering from severe bleeding episodes and knee muscle contractures. He was an engaging youngster whose parents seemed to reject him because of his physical condition. F. B. compensated for this rejection by being very ingratiating towards others. He involved himself in wild drinking bouts, experimented with drugs, and would participate in physically demanding activities. During counseling sessions, F. B. would commit himself to a behavior change, but on returning to his community, he was powerless in controlling his destructive impulses. It was a problem in therapy. In fact, our efforts ended in failure. F. B. struggled through high school and refused vocational training or meaningful employment. He was content to do nonpaying volunteer work for the hospital, resisting all efforts to place him in an outside job. He was finally hospitalized in the psychiatric ward for a period of three months. By this time, his parents wanted no part of the young man, so F. B. was placed in a residential treatment center with the responsibility of his care transferred to the center's personnel. A plan was devised where F. B. would receive blood replacement products from a hospital near his new residence. Reports filtering back to the clinic indicated that F. B., as usual, had antagonized staff members, peer groups, medical and professional personnel, and community people. The center's staff reports that they did not know what to do with the young man and were unable to be of help. F. B. has been exposed to good medical care, casework, psychiatric and vocational rehabilitation services. However, he seems unable to utilize these services in order to improve the quality of his life. It is the counselor's opinion that F. B. will be in and out of institutions the rest of his life.

Discussion

Present clinical evidence indicates that early detection along with careful medical, dental, social, psychological, educational, and vocational planning can help the hemophiliac lead a normal, rewarding life. With planned treatment, there is no problem getting the hemophiliac patient through a meaningful educational program, whether it be high school, trade school or college. The problems are in convincing insurance companies, employers, fellow employees, company doctors and family members that the hemophiliac patient as an employee can be a person with few, if any limitations and a productive worker. This means the counselor has to eliminate fears about the bleeders' disease by informing people of modern medical techniques such as blood replacement therapy, home care, physical therapy, dental treatment, and surgery which greatly enhance the hemophiliac's physical capacities.

People become advocates of improving the conditions of the hemophiliac patients when they thoroughly understand the present state of the field. The vocational rehabilitation counselors, with the cooperation of team members, have visited employers who had rejected patients because of their medical condition. It was explained to them that a patient, as an employee, could infuse himself, if necessary, during break time or lunch periods or could continue his work schedule until closing time, then travel to a nearby hospital for treatment or treat himself at home. Productivity need not be negatively affected nor need the employer or other employees be concerned that a hemophiliac will bleed to death because he works with heavy equipment and chemicals. On understanding the treatment of hemophilia, employers have hired patients with long-term positive results in fields such as air conditioner and computer repair and in electronics.

The counselor has invited groups of professionals from the Workman's Compensation Board, Office of Vocational Rehabilitation and New York State Employment Service to visit the Mount Sinai Hospital Hemophilia Clinic and participate in a panel discussion with team members. Results have shown a positive attitude change toward hemophilia by persons participating in these panels. They now readily accept the hemophilic patient as a client and have been instrumental in obtaining suitable employment for them.

Improvement of educational and employment opportunities for the hemophiliac have also been helped by the introduction of home care and surgical procedures. Now the patient can infuse himself at home, doing away with long, painful hospital stays and allowing the patient to spend more time in school and at work.

Surgical procedure to correct impairments has enabled the patient to return to school or work much earlier than previously, limiting the risk of the person losing their job or valuable school time. However, a great deal of study needs to be done in vocational rehabilitation for the hemophiliac with medical complications that result in frequent absences and interfere with regular employment. The solution to the problem may be the use of sheltered workshop, private employment, or the creation of special job categories by government or private industry.

"It is not the hemophilia but the attitudes of people towards hemophilia that retards the development of the hemophiliac child" (6). Ideas often repeated in literature tend to become fixed in the minds of both professionals and nonprofessionals. It is these archaic attitudes towards the patient suffering from what used to be called the bleeders disease that have to be changed. "If a professional counseling service were readily available at the time of diagnosis and thereafter, parents would have the opportunity to explore their reactions to the handicapped child, to gain emotional support during crisis, and to learn to plan and provide a home climate that fosters independence and growth. This preventive approach would reduce the necessity for rebuilding a damaged self-image in adulthood" (7). "We must remember that the hemophiliac is first a person, and secondly a person with hemophilia. Although hemophilia cannot be cured, it can be so minimized as a health disability that the life expectancy and life style of the hemophiliac born in the 70's is that of his peers. Early, appropriate, aggressive treatment will normalize the life and living of the hemophiliac . . . " (3). New therapies that enable the patients to lead normal lives need to be brought to the attention of those who occasionally treat a hemophiliac patient, so that all patients can reach their maximum potential. Hemophiliacs cannot and should not be pigeonholed into a few job categories for they have shown that, if given a chance, they can successfully work in a wide variety of jobs.

References

1. Isarn, P.: Social and Vocational Rehabilitation of Hemophiliacs, Wisconsin Med J 66:336, 1967.
2. Britten, M.: The Hemophiliac Boy in School, J Biosocial Sci 2:224, 1900.
3. Bedard, L. D.: Education and Employment of Hemophiliacs. In *Hemophilia: A Canadian Handbook*. 1900, p. 39.
4. Taylor, C.: Hemophilia Center at Work, Rehabilitation Record, 1900, p. 4.
5. Katz, H. A.: A Study of Hemophilia, Am J Pub Health, 53:1672, 1900.
6. Rusalem, Problem in Vocational Development of the Hemophiliac Individual, Bibl Haem, No. 34, P. 213.
7. Katz, A. H.: Social Adaptation in Hemophilia, School of Public Health, University of California at Los Angeles.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May–June, 1977
Printed in U.S.A.

Lesson Plan for Self-Treatment in Hemophilia

JUDITH BEST, R.N., M.A.

Within the scope of the comprehensive home treatment program, the nature, mode and implementation of the home care lesson plan assumes major significance. The lesson plan must be designed to address the needs both of adult and adolescent patients, with care being taken to assess the learning level of the individual patient prior to enrollment in the teaching program.

The lesson plan is designed to teach the technique of self-administration of clotting factor concentrates for the purpose of factor replacement therapy in the hemophilia patient.

It is estimated that there are 25,000 hemophiliacs in the United States with a population occurrence rate of one out of every 10,000 individuals being affected. Since the nature of the disease traditionally required long periods of hospitalization, the concept of self-treatment with factor concentrates has emerged in an attempt to alleviate the acute symptomatic presentation of each bleeding episode, as well as to diminish secondary complications resulting from such bleeds.

The implementation of such self-treatment programs has become a reality in light of the commercial availability of clotting factor concentrates. This product availability has provided a basis of management for the patient within his own home whereby the prompt and accurate administration of the appropriate concentrate results in quick cessation of the bleeding episode, often with a temporary correction of the clotting dysfunction.

With such advances in the treatment of patients with clotting factor disease, there is every reasonable hope that the hemophiliac can escape severely crippling deformity and subsequently live a life of relative normality.

As indicated above, home transfusion is dependent upon the availability of factor concentrates which obviate circulatory overload due to plasma or whole blood therapy frequently employed in the absence of commercial products. Inasmuch as cryoprecipitate provides an equivalent amount of Factor VIII activity as do commercial products, the necessity for pooling of product and of refrigeration negates its lower cost factor. Thus it is seen that the most reasonable choice for patient self-administration is clotting factor concentrates, available through several drug suppliers throughout the United States.

The implementation of the actual treatment regimen is based either on prophylactic or episodic need for replacement of deficient factor. The latter treatment plan is selected most often because it facilitates the economical

From the Mount Sinai Hospital Hemophilia Diagnostic and Treatment Center, New York, N. Y. 10029.

utilization of blood products while at the same time affording the patient the necessary treatment at time of need.

Statistics collected over the period of July 1, 1975 to June 30, 1976 reveal a population of 183 hemophilia patients registered at The Mount Sinai Medical Center (1). From this registered population, a selection protocol is implemented by the multidisciplined hemophilia health care team to screen eligible patients who are emotionally capable of assuming self-care responsibilities, as well as exercising discriminative judgment in the application of self-treatment.

Based on the above, this lesson plan is designed for emotionally appropriate individuals or responsible family members who have been screened for participation in the home care treatment program. The teaching sessions are designed for one-to-one teacher demonstration, and learner participation. The actual demonstration-learning program which evolves through various methods of content delivery is specifically intended for one-to-one implementation. Use of discussion, teacher demonstration technique, and learner practice progresses in an orderly fashion based on the design of the specific content objectives, as well as the learner's ability to progress from one content phase to the next.

A small office demonstration laboratory provides the teaching setting. Learning tools such as needles, syringes, vials of saline, demonstration medication vials, an artificial arm, IV apparatus, alcohol wipes, and tourniquet are used.

Terminal Objectives

Upon termination of the teaching program, the patient-student or significant family member is expected to:

1. State, in order, the procedures to be taken in the event of a bleed, according to steps outlined in instructional content.
2. State the principles of how and why these procedures are performed, according to instructional content.
3. Verbally enumerate and differentiate the clinical signs and subjective symptoms that are:
   a. amenable to self-administration of concentrate factor; or
   b. require emergency room care, as delineated in instructional content.
4. Administer factor concentrate by demonstrating preparation of product including:
   a. preparation of correct dose;
   b. use of safe and effective technique for:
      1. IV administration;
      2. disposal of infusion hardware, as presented in teaching sessions.

Specific Objectives

I. Upon completion of the demonstration and learning program, the learner will:

1. Demonstrate aseptic technique by:
    a. giving hand washing demonstration;
    b. swabbing concentrate vial tops;
    c. cleansing injection site with betadine or alcohol wipe, according to teacher demonstration.
2. Verbally state his own specific factor deficiency as validated in his physical history record.
3. State, by product name, factor concentrate available for replacement therapy for his specific factor deficiency according to medical consultation.
4. State clinical indications for:
    a. home therapy;
    b. emergency room care, according to previously stated medical guidelines.
5. State the known side effects of infusion materials to be administered, according to product packaging information.
6. State the recommended treatment for the side effects indicated above according to standard medical practice.

II. Given several brand name product demonstration vials, the learner is expected to:
1. Examine product labeling and state product potency according to labeling information.
2. Demonstrate with pencil and paper, calculation of the correct dosage for each product according to doctor's prescription.
3. Demonstrate reconstitution of concentrate factor for self-administration by adding dilutent and drawing solution contents into 50 cc syringe.

III. The learner will demonstrate venipuncture technique by:
1. Applying tourniquet, on self or demonstrator arm, and palpate for suitable vein according to teacher demonstration.
2. Satisfactorily enter vein with IV apparatus as measured by adequate blood return.

IV. Learner will demonstrate correct infusion technique by:
1. Connecting syringe filled with factor to indwelling IV apparatus and administering the factor concentrate over a 10 minute period of time.

V. Upon completion of the infusion, the learner will:
1. Demonstrate removal of IV apparatus, and achievement of hemostasis at infusion site as evidenced by cessation of blood flow from puncture site.
2. Demonstrate disposal of all injectable materials according to previously stated safety measures.
3. Summarize in writing the data of the bleeding episode as outlined on the bleeding episode log.
4. Verbally evaluate the effectiveness of the self-treatment by reciting the signs and symptoms which are indications of:
    a. successful self-treatment and/or
    b. need for additional medical consultation.

TEACHING METHOD AND LEARNING EXPERIENCES

The method selected for teaching and implementation of the specific objectives is individualized instruction. De Thornay points out that individualized instruction addresses the diverse learning abilities as well as different learning speeds of individuals. It allows for formal education with supervised experience tailored to independent learning. It presumes formulating problems of the learning situation, finding solutions to implementation, and evaluating learner progress. The selected instructional materials serve to aid the learner in achieving autonomy of thought and action (2), which in fact is the underlying goal of the home treatment program.

As with all other forms of instruction, individualized instruction requires planning. The success of the instruction demands clearly outlined goals prior to each meeting. Hence the lesson implementation has been broken down into a long-range meeting plan, the nature of which will allow for supervision and reinforcement.

For the purpose of delineation, a major comprehensive objective is selected to define the nature of the learning experience:

1. Given three different product demonstration vials, the learner will handle concentrate vial to become acquainted with vial appearance, and location of product potency on each label so as to be able to evaluate unit dose by brand name.
2. Given the dosage calculation equation, the student will perform pencil and paper calculation until, given any product potency, he can easily calculate the correct prescribed dosage necessary for infusion for major and minor bleeds.
3. Given a single vial, the learner will practice removing protective covering from vial top and thus demonstrate aseptic technique by:
   a. practice swabbing vial top with antiseptic swab.
   b. practice puncturing vial top with needle and syringe, until comfortable with experience.
   c. practice drawing dilutent from vial into syrings and re-expressing fluid from syringe into vial until comfortable with procedure.
   d. practice extracting dilutent from one vial and injecting into powdered concentrate, simulating reconstitution of factor until comfortable with procedure.
   e. practice drawing liquid content from vial into 50 cc syringe without contaminating vial contents or needle until comfortable with procedure.

Since the specific practice materials are available for the student-patients use and experience at all times during planned meetings, the student-patients are allowed the opportunity to become fully acquainted with the materials and learning tools listed above. Injection technique is initially practiced on an artificial arm until the student demonstrates both comfort and competence for self ven puncture. The major role of the nurse teacher is to provide guidance and support, as needed.

Prior to the implementation of specific discussion and demonstrational content, a survey of the student's comprehensional and skill ability is elicited by asking the student to state his knowledge and demonstrate his skill. Upon assessing the learner's command of accurate knowledge and skill, the nurse clinician decides the appropriate placement of the student within the learning context. A criteria of assessment includes having the student state his understanding of his disease and reasons for home treatment, as well as a statement of anticipated outcomes of self-treatment and home care. In a continual interaction with the student, the nurse clinician seeks to:

1. Analyze the skill before attempting to guide the learner.
2. Demonstrate the skill correctly.
3. Guide the initial practice attempts verbally and, if necessary, physically.
4. Provide for practice.
5. Encourage additional periodic practice.
6. Let the learner know what he is doing correctly and what he needs to improve (3).

After an initial interview with the patient, and when present significant family members, it becomes evident how much time is actually required to implement the stated objectives. In short, this simply means that, based on the individual's comprehensional and skill level, some patients will require more formal demonstration and reinforcement than others to attain a level of confidence consonant with the stated goals of self-treatment.

In any case, the core content which is derived from the stated objectives should be implemented in distinct phases so as to allow for feedback and return content and demonstration on the part of the patient to the nurse teacher. Again, for some individuals, several or all of the phases may be combined into one or two lengthy meetings, while for other patients it may be necessary to meet with them on an ongoing basis until both teacher and patient are confident that the home treatment can be properly managed by the individual.

In general, it is wise to initially meet with the patient and as many family members as is possible to discuss with them what hemophilia has meant to the individual patient, as well as to the family. This meeting is intended to allow the patient to verbalize how he perceives his life style and, based on his past experiences with treatment through emergency facilities, to come to grips with how his life style might be modified to his current treatment availability. It is at this point that a discussion of the benefits of self-treatment is most appropriate, for although it may not alter the life style of an individual, it certainly allows for more latitude within the particular living style. It should be made clear to the patient about to embark on self-care that although he will ultimately be responsible for his own treatment, a consultative liaison with his treatment center will always be encouraged.

For this reason, it is vital for the patient to be very clear on the clinical signs and subjective symptoms which are amenable to self-treatment, and those that require emergency room care. Since each patient will manifest different bleeding patterns, care must be taken on the part of the nurse to establish with the patient individual guidelines for interpreting individual bleeding episodes in terms of major and minor bleeds.

A graphic representation of a typical joint is useful to illustrate the bleeding process into the joint space with the attendant inflammation and swelling. Further diagraming will clarify how orthopedic damage results over time, thereby enforcing the need for prompt and accurate assessment and treatment of the bleeding episode. It is also significant at this point to discuss the clotting mechanism at a level appropriate to patient's comprehensional skill. Again, diagramatic representation is useful, both in indicating the cascading effect of the clotting mechanism, as well as the process by which blood is absorbed at the site of a bleed.

After the nurse has allowed for discussion and questions on the part of the patient and family, it is appropriate to begin a discussion on the concentrates used for home-treatment, and then as a reinforcement of the above, explaining how they function as an aid in clotting deficiencies. Cautioning the patient about the risk of the transmission of hepatitis in the use of concentrate products, a discussion of aseptic technique follows with a demonstration of hand-washing technique. It is wise to instruct the patient to procure a tray or a plastic shoe box in which he can store all his equipment. At this point, the nurse demonstrates the equipment which is to be kept on hand for the home infusion, and urges the patient to maintain all his supplies in one place so that at the time of a bleed he will not find it necessary to search for needed equipment. The nurse then suggests an arrangement of infusion hardware and concentrate for use during the treatment and encourages the patient to place his equipment in such a way that it is both convenient and accessible to him at the time of infusion.

If the patient has not had experience with infusion hardware, he is encouraged to handle all the necessary equipment. The nurse should take the time to demonstrate the technique for drawing up fluid and aspirating solution from one vial to another before the patient is given a syringe and allowed to practice the procedure. The patient is then instructed in cleansing of vial tops and the maintenance of sterile technique in the handling of needles. A demonstration of the reconstitution of concentrate follows, with the learner returning the demonstration.

Teaching of the venipuncture technique follows with demonstration of the application of the tourniquet and selection of a vein appropriate for venipuncture. The patient is urged to select a vein which is straight and does not have a tendency to roll. He is further encouraged to delineate the vein with a washable fine point magic marker so as to visually reinforce in his mind the location of the vein selected for venipuncture. After the patient has had sufficient experience with venipuncture on the artificial arm, the patient is instructed in the cleansing of the venipuncture site, and then guided to do self-venipuncture under the nurse's supervision.

At the conclusion of the teaching session, the patient is expected to reconstitute his product, select a suitable vein for infusion and demonstrate for the nurse the actual infusion of concentrate product. An explanation of record-keeping will be demonstrated, with the patient being given a bleeding log to record his bleeding episodes, as well as to keep an accurate record of the amount of produce being used.

Potential emergencies which may arise at home will be reviewed, with the patient again being reminded of the liaison that is expected to be kept by himself and the supervising institution. In cases where patients may require, for other medical reasons, additional medications for infusional use, the time of a pharmacist may be employed to discuss with the patient the cautions of intermixing IV solutions. In some cases, it may also be appropriate to have available other medications which they may be required to use, advising them of unexpected side effects of such drugs.

With the dispensing of supplies, an arrangement must be made between the patient and the treatment center to have the patient evaluated medically on an ongoing basis. For this reason, it may be decided that in cases where patients are using large quantities of concentrate that a three month follow-up by the health team may be necessary. In other cases, a less frequent follow-up may be adequate with additional material being supplied at the time of completion of a bleeding log.

Since, as Reilly states, "evaluation is related to objectives and is delineated in terms of measurable student behavior" (4) summative evaluation will be gauged against the mastery of stated objectives with requirement for performance being contained within their statement. Hence, various methods of evaluation will be based on student return demonstrations, pencil and paper computation performance, and recitation of qualified academic content.

Because of the nature of the disease and variation in individual severity, certain student self-evaluation criteria will vary depending on the severity of their own symptomatology. Thus, in all cases, evaluation of objective achievement will be based on individual history.

References

1. Aledort, L. And Gilbert, M.: Project Narrative of Proposal for Comprehensive Hemophilia Diagnostic and Treatment Center Project, Mt. Sinai Medical Center, New York City 1976.
2. deThornay, R.: *Strategies for Teaching Nursing*. John Wiley and Sons, Inc., New York 1971, p. 102.
3. Klausmeier, H. J. and Goodwin, W.: *Learning and Human Abilities*, 2nd ed. Harper and Row. New York 1966, p. 321–322.
4. Reilly, D.: *Behavioral Objectives in Nursing Evaluation of Learner Attainment*. Appleton-Century-Croft. New York 1975, p. 89.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 3, May-June, 1977
Printed in U.S.A.

Epilogue

LOUIS M. ALEDORT, M.D.

Since the discovery of cryoprecipitate, the diagnosis and appropriate treatment of hemophilia have attained great sophistication. Components of health care for hemophiliacs are reiterated throughout this monograph. They are the ability to diagnose appropriately, provide material for treatment, and provide the financial support for the delivery system.

In many countries the problem is more a matter of health priorities than of not having the tools either to diagnose or treat the disease. Many nations have neither an appropriate blood delivery system nor trained personnel so that blood and its products are not available to the population. In addition, few countries have provided any financial support for a hemophilia care program. Iran, for example, had no program a little more than five years ago. A workshop held in that country focused attention on the problems of hemophilia and thus created a milieu for the naissance of a hemophilia program. In those countries in which priority is not a problem, and material as well as financial support are available, (e.g., Italy and France) one is beginning to see effective coordinated comprehensive care.

In America it has clearly been shown that the solution to the hemophilia problem rests with giving it high priority. At present, sixteen states provide some financial support above and beyond third-party payment for the treatment of hemophilia. However, there is still inadequate financial support of this very expensive disease. Services are variable from city to city. Most regions in the country do not have a coordinated hemophilia program, although there are knowledgeable personnel in comprehensive care for the hemophilia patient in many places.

In addition, we face a major problem in blood delivery. Although we have multiple means for collecting, fractionating and utilizing component therapy—i.e., the ability to break down a single unit of blood into many products such as plasma and white blood cells for providing materials—we have not yet achieved a national blood policy. The American Blood Commission is a private-sector movement which is charged with attempting to develop such a policy. Its aim is to produce an all volunteer system. This would provide the materials to support the needs of patients with coagulation defects as well as the population at large.

Until this is done, we face episodic shortages in material as well as long-range inability to meet the demands of hemophiliacs. The United States produces most of the fractionated Factor VIII and IX materials in the world. At present, industry cannot supply the needs of hemophiliacs in the United

From the Department of Medicine, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

States and the rest of the world. Therefore, we must consider the United States as a part of the total world's needs.

If one were to look at the future, the hemophiliac's biggest problem is the lack of comprehensive care facilities. It is the hope that Part D of Section 1131(a) of Public Law 94-63, creating hemophilia treatment centers, will provide sufficient programs of comprehensive care. The most important part of the concept of comprehensive care is not only that the team provide community services, but that it provide the vehicle for the continued delivery even if the patient lives far away from the center. Thus the physician caring for that patient can be made aware of therapy that is tailored for that given patient. Such a comprehensive system must be coordinated with the blood delivery system so that one is constantly aware of the impact that hemophilia care makes on the blood supply.

Although a totally coordinated program throughout the United States for all hemophiliacs is a goal which may not be realized for many years, this country has made major strides in the diagnostic and therapeutic aspects of hemophilia. The comprehensive care program at Mount Sinai School of Medicine is a prime example of the ability to deliver good care to a large number of patients. Our hope is that this model can be utilized to set up other programs both here and abroad. Our commitment to optimal utilization and delivery of blood products will hopefully provide a data base so that one can extrapolate to other parts of the United States and to the rest of the world. We must be able to predict how much material is needed, how much it will cost and how to develop comprehensive care programs.

Many problems confront the hemophiliac in being able to meet the cost of care. Not enough is available regarding the analysis as to who pays the actual dollar costs of care plus replacement material. The out-of-pocket expenses can only be guessed at in most cases. The indigent now have Medicaid in most areas of the country. Those totally disabled by the disease for more than two years are eligible for Medicare. Children can receive benefits from various agencies such as the Crippled Children's Bureau. These programs are spotty in their ability to give financial support and thus one cannot develop a generalized statement about these agencies. Third-party payers vary substantially in their policies regarding payment for the use of blood and its products. In addition, many will only pay for use in a hospital or in an outpatient facility.

Only in those areas where there is broad-base coverage by one insurer, or where hemophilia chapters have educated and worked closely with these payers, have total coverage programs developed. In one study (1) $320 was the average out-of-pocket expense per patient per year. However, only three of these seventy-two patients had no means of outside financial support. Even in this group, eleven of seventy-two patients had unpaid bills in excess of $1,000, and one was $13,500.

Through the efforts of those dedicated to solving the hemophilia problem in this country, sixteen states have developed programs to meet some of the uncovered costs of hemophilia products. It is too early to measure the long-term effects of such programs. It is clear, however, that we lag far behind many countries where hemophilia care and replacement materials are fully supported by government programs.

References

1. Levine, P. H.: Efficacy of Self-Therapy in Hemophilia. A Study of 72 Patients with Hemophilia A and B, N Engl J Med 29:1381–1384, 1974.

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Functional and Morphologic Studies of the Effect of Alcohol on the Pancreatic Parenchyma

ORLANDO BORDALO, M.D.*, MANUELA NORONHA, M.D.†, AND DAVID A. DREILING, M.D.‡

In the early 1950's clinical and investigative data discredited the classical theory of pathogenesis of pancreatic inflammation, the hypothesis of "common channel" with biliary reflux. In its place, based upon anatomic findings, physiologic studies, and clinical associations, the "Big Duct Theory of Pancreatic Obstruction" emerged. According to this hypothesis inflammation developed according to the following sequence:

1) increased secretion of the gland
2) against obstruction in a major duct
3) leading to ductular hypertension
4) with rupture of ductular radicals
5) extravasating activated pancreatic ferments
6) into the pancreatic interstitium
7) where inflammation was initiated by chemical autodigestion.

From the very beginning the "Big Duct Theory" failed to account for:

1) the long incubation period of years between the inception of alcoholism and the initial attack of acute pancreatitis,
2) the absence of big duct obstruction in many cases of acute alcoholic pancreatitis,
3) the negative correlation between alcoholic cirrhosis and alcoholic pancreatitis,
4) a duration-dose dependency between alcoholism and pancreatitis, a relationship more suggestive of metabolic disorder than mechanistic derangement.

Intense physiologic studies in man and experimental animals have partly resolved these dilemmas and have resulted in a repudiation of the "Big Duct Theory." These studies showed:

1) that the response of the pancreas to minimal injury was hypersecretion of electrolyte and protein,
2) that the hypersecretory state was associated with pancreatic ductular hypertrophy/hyperplasia and reduplication, a pathologic process which

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* Professor of Medicine, Faculty of Medicine of Lisbon, Head of Pancreatic Section, Lisbon, Portugal. This paper was presented October 21, 1976 as the Ralph Colp Lectureship of the Department of Surgery, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

† Assistant of Surgery, Faculty of Medicine of Lisbon.

‡ Professor of Surgery, Mount Sinai School of Medicine of The City University of New York

was reversible or might progress to necrosis, fibrosis, and/or pancreatic atrophy depending upon the cessation or persistence of alcoholism.

It was the brilliant research of Sarles and his group (1) and the parallel investigations of Dreiling and Bordalo (2) which accomplished a synthesis of this physiologic data with the formulation of the "Small Duct Hypothesis." Sarles stressed the protein hypersecretion and demonstrated proteinaceous plugs blocking the smaller ducts with disorganization and disruption of the ductules. The data of Dreiling and Bordalo (3–5) supported these findings but stressed hypersecretion of fluid and electrolyte with alterations of ductular membrane permeability permitting back diffussion of enzymes.

The growing awareness of alcohol as a general cellular toxin, affecting the liver cell, the nerve cells and their axones, the smooth and cardiac muscle cells, the epithelial cells of the gut as well as the disclosure of biochemical mechanisms of toxicity to the liver cell by Lieber with the electronmicroscopic demonstration of cellular fatty degeneration, endoplasmic reticular hyperplasia, mitochondrial disruption that strongly suggested to us that alcohol might act as a direct metabolic toxin to the pancreatic parenchymal cell.

The following investigations were designed to pursue the possibility of toxic metabolic pancreatitis.

Two groups of alcoholic patients, those with and without clinical and morphologic evidence of chronic pancreatitis were studied. The 42 patients in this preliminary series were divided as follows:

1) chronic alcoholics without pancreatitis – 10 cases
2) patients with chronic alcoholic pancreatitis – 20 cases
3) patients with nonalcoholic pancreatitis – 12 cases

Light, thin sections and electronmicroscopic preparations were made on surgical biopsies performed in the most grossly normal areas of the gland and these were compared with similar preparations made in a group of patients with nonalcoholic pancreatitis.

The morphology findings showed significant differences among these groups of patients. Specimens from chronic alcoholics without pancreatitis revealed, in some cases, a normal histologic appearance. In other cases, characteristic morphologic abnormalities were noted, viz., in light and thin sections microscopy, cellular degeneration and accumulation of fat droplets in acinar cells. These droplets varied in size from small to big cyst-like vacuoles. The cells with fatty degeneration displayed a parallel decrease in zymogen granules. Less frequently centro-acinar and ductular cells showed fatty accumulation but without evidence of cell degeneration. Signs of ductular reduplication were present and peri-ductular fibrosis was occasionally found. No protein plugs were observed. In general, the lobular architecture was preserved. Electron microscopy specimens in this group showed ultrastructural changes, viz., dilation and vesiculation of the endoplasmic reticulum. The cells frequently contained a fibrillar curved osmeophilic material assuming the appearance of myelin-like fibers, surrounded by an irregular clear area of granular substance. Less frequently the mitochondria were enlarged and revealed distortion of the mitochondrial cristae. The greater the alcoholic consumption the more conspicuous the abnormalities found.

Light and thin section specimens taken from patients with chronic alcoholic pancreatitis, disclosed in addition to these abnormalities:

1) acinar atrophy
2) signs of ductular hypertrophy and metaplasia
3) acinar canalization
4) areas of peri-ductular and septal fibrosis

These findings, although focal, disturbed the normal architecture of the gland. The acinar ultrastructure, besides the alterations of endoplasmic reticulum and mitochondria described for the group of alcoholics without pancreatitis, disclosed autophagic vacuoles and areas of cytoplasmic sequestration enclosing zymogen granules. Sometimes, the endoplasmic reticulum assumed a spiral shape, characteristic of cell regeneration. Ultramicroscopic alterations of ductular cells were negligible.

In the group of non-alcoholic pancreatitis, these abnormalities were not found.

Based on morphology, it seems evident that the first response of the pancreas to alcoholic injury is fat accumulation within parenchymal cells. This could be due either to a direct toxic effect of ethanol, through a metabolic pathway, such as in the liver, or to an indirect effect, by means of an alcohol-induced hyperlipemia. Against hyperlipemia are serum lipid determinations made in the 50 chronic alcoholics, after a seven-day period abstinence. Hypertriglyceridemia was present in only one case. No significant changes were noted in very low density lipoprotein fractions, fractions most affected in acute administration of alcohol. Moreover, no fat accumulation was observed in hystiocytes of pancreatic intestitial tissue. The presence of small amounts of ADH, the increased number of peroxisomes, and the mitochondrial aberrations, suggest a direct metabolic effect of alcohol on the pancreatic cells and could result in metabolic alterations leading to an increased NADH/NAD ratio. Excess of liver-produced acetate, carried by the blood to be metabolized extrahepatically, could be another explanation.

Our findings demonstrate the acinar cell to be the structure primarily affected by chronic ingestion of alcohol. Fatty accumulation may initially be a normal and appropriate response and, therefore, reversible. Signs of cellular degeneration and decrease of zymogen granules appear with increasing fat droplets. In this stage of pathology, small amounts of fat may appear within ductular cells. Ultrastructural changes, especially those in the endoplasmic reticulum, e.g., myelin-like figures, could represent not only the toxic effect of alcohol on cytomembranes as it is found in the liver of alcoholics, but also a possible inhibition of synthesis of polypeptides on membrane-bound polyribosomes.

Ductular reduplication may represent the reaction of the cell to fat accumulation or result from a direct toxic effect of alcohol. This morphologic step is responsible for fluid and bicarbonate hypersecretion. Paradoxically at this stage enzymes are within normal ranges indicating acinar cell regeneration, a reaction supported by the spiral shape of endoplasmic reticulum observed in some cells.

Development of extensive fibrosis around ducts as well as ductular hypertrophy and reduplication causes ductular obstruction, stasis and, therefore, protein plug formation.

Finally, distortion of the glandular architecture in addition to continuing ductular obstruction results in atrophy of acinar tissue and metaplasia of ductular cells with its pattern of pancreatic insufficiency.

Bibliography

1. Sarles, H.: Chronic Calcifying Pancreatitis—Chronic Alcoholic Pancreatitis, Gastroenterology 66(4): 604–616, 1974.
2. Bordalo, O., Batista, A., Noronha, M., Lamy, J., and Dreiling, D. A.: Effects of Ethanol on Liver Morphology and Pancreatic Function in Chronic Alcoholism, Mount Sinai J Med 41(6):722–731, 1974.
3. Dreiling, D. A., and Bordalo, O.: Secretory Patterns in Minimal Pancreatic Inflammatory Pathologies, Am J Gastroent 60(1):60–69, 1973.
4. Dreiling, D. A., Greenstein, A., and Bordalo, O.: Newer Concepts of Pancreatic Secretory Patterns. Pancreatic Secretory Mass and Pancreatic Secretory Capacity: Pancreatid Hypersecretion, Mount Sinai J Med 40(5):666–676, 1973.
5. Dreiling, D. A., Greenstein, A., and Bordalo, O.: Comparison of Standard and Augmented Secretin Test Responses in Pancreatic Disease Delineation of the Pancreatic Tubular Cell Mass and Its Alkaline Secretory Capacity, Am J Gastroent 61(6):433–442, 1974.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

A Critique of the Criteria for the Diagnosis of Diffuse Malignant Mesothelioma

MILTON KANNERSTEIN, M.D., W. T. ELLIOTT McCAUGHEY, M.D., JACOB CHURG, M.D. AND IRVING J. SELIKOFF, M.D.

Abstract

The determination of the histogenesis of complex, atypical or undifferentiated neoplasms requires the employment of parameters supplementary to the microscopic morphology. On the basis of their collective experience the present authors regard this principle as particularly relevant to the diagnosis of diffuse malignant mesothelioma, which has an almost uniquely broad spectrum of cytohistologic appearances. The additional elements of information – one or more of which may be necessary – include the gross morphology, histochemistry, the chemistry and cytology of effusions, ultrastructure and clinical and radiographic features, with those exclusionary of another possible origin. When certain aspects are noncharacteristic or apparently contradictory the diagnosis must be qualified. The degree of certainty should be specified in the diagnostic statement. The association of mesothelioma with asbestos demands a reliable monitoring of trends in incidence.

It has been general experience that in the decision as to the histogenesis of neoplasms elements of information beyond the microscopic morphology may be required. The more complex, atypical or undifferentiated the tumor and the more essential precision of diagnosis, or at least an estimation of the limitations of certainty, the greater the quantity of information that is likely to be needed. An example of this situation is mesothelioma of the pleura and peritoneum.

Over a period of years the authors have had the aggregate experience of studying approximately a thousand cases diagnosed as mesothelioma, with varying degrees of certainty, or tumors simulating mesothelioma and rejected. This experience has led to the considerations presented here.

The causal association between asbestos and diffuse mesothelioma of the pleura and peritoneum requires an accurate epidemiologic monitoring of the incidence of this neoplasm (1-5).

The increasing number of cases and a voluminous literature have led to greater familiarity with its characteristics on the part of clinicians and

From the Departments of Pathology, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029 and the Barnert Memorial Hospital Center, Paterson, N.J. 07514; the Canadian Tumour Reference Centre, University of Ottawa, Ottawa, Ontario, Canada KIN 9A9; and Environmental Sciences Laboratory, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Supported by U.S. Public Health Service Grants No. AM-00918, National Institute of Arthritis, Metabolic and Digestive Diseases and ES-00238, National Institute of Environmental Sciences.

Requests for reprints should be sent to: Milton Kannerstein, M.D., Department of Pathology, Barnert Memorial Hospital Center, Paterson, N.J. 07514.

pathologists. However the diversity and complexity of its micromorphology and an overlap of clinical and gross pathologic features with those of certain visceral and soft tissue neoplasms metastatic to the serous membranes appear to complicate the problems of diagnosis. A few published studies (6, 7, 8) and our own experience on national mesothelioma panels indicate that a meaningful proportion of submitted cases are unacceptable. There is reason also to believe that an undetermined number of cases of mesothelioma are not recognized, although this aspect is not well documented (5, 9, 10). Thus the possibility exists of a significant over- or underestimation of the frequency of these tumors and the implication that the determination of future trends in incidence may be obscured. It would appear that diagnostic assessment of the individual case of possible diffuse mesothelioma must depend on the weighing of a variety of evidential factors, clinical as well as pathologic, and the rendering in some cases of a less than definite opinion.

We shall attempt here a brief evaluation of the parameters that relate to diagnosis. These consist of clinical history, chemical and cytological study of effusions, gross pathology as demonstrated by exploratory surgery or autopsy and, most important, the cytohistologic features including histochemistry and ultrastructure. For detailed descriptions and discussions of each of these aspects the reader is referred to the many excellent publications, some of which are listed in our references. Localized mesothelioma, and the rare primary mesotheliomas of the pericardium and tunica vaginalis testis are not considered.

Clinical Features

These are relatively stereotyped and when these are present diffuse mesothelioma should be included early in the differential diagnosis. Constitutional symptoms such as weight loss (11-13), lassitude, and fever are common. In pleural tumors chest pain, shortness of breath and cough are often initial complaints and evidence of effusion is the commonest initial finding. Chest x-ray may show a pseudolocalized mass or masses or diffuse thickening of the pleura. In peritoneal tumors abdominal discomfort or actual pain and gastrointestinal disturbances are the usual presenting complaints. Ascites is generally evident (14, 15, 16). In both instances evidence of extension in various directions can often be determined by clinical and radiographic means. In the pleura this may follow a rather characteristic course with invasion of the chest wall, diaphragm and mediastinum and contraction of the involved hemithorax. In the abdomen the viscera become matted together and localized masses often are palpable. Evidence of intestinal obstruction may develop. Unlike many visceral tumors which can produce very similar signs and symptoms metastases from a mesothelioma are seldom evident during life. The clinical course of diffuse mesothelioma of the peritoneum is even less specific than that of the pleura in that many different types of abdominal malignancy evolve in a similar manner. While the majority of cases of mesothelioma, pleural and peritoneal, die in less than one year from onset of symptoms, a few survive for considerably longer periods.

Effusions—Chemistry and Cytology

The presence of the acid mucopolysaccharide (AMP) hyaluronic acid (HA) in the effusions produced by mesotheliomas has been regarded as of definite diagnostic value by a number of investigators (17–19). With more sensitive methods AMP will be detected in most mesotheliomatous effusions but also in fluid of other etiologies, although in the latter the AMP may be a chondroitin sulfate rather than HA (18). With less sensitive procedures AMP will be detected only in those mesotheliomas producing larger quantities (19). It would seem that a concentration of AMP of over 120 μg/l which can be demonstrated to be HA is suggestive evidence of mesothelioma but must be correlated with cytology or biopsy for diagnosis.

The cytology of effusions caused by mesothelioma varies from the undifferentiated to the highly differentiated, often consisting of admixtures of these types (20). The nucleus, as in general, is the index of the malignant character of the cell. The extent to which the cytoplasmic features and the intercellular articulations resemble those of normal mesothelial cells is the degree to which origin from mesothelium is revealed (21, 22). The most frequent problem is the distinction between well-differentiated mesothelioma cells and the cells of reactive hyperplasia. If solely undifferentiated cells are present histogenesis cannot be specified. However, the latter constitute a minority of cases (20, 23).

Most writers on the subject have concluded that malignant mesothelial cells can be identified as such with reasonable certainty in the majority of cases. They had a few false positives and false negatives. The question as to whether tissue confirmation is essential is commented on by Naylor (21). He states that the combined cytologic and chemical approach to the diagnosis of diffuse malignant mesothelioma has been so successful that it has largely eliminated the need for diagnostic thoracotomy or celiotomy at his institution. Undoubtedly, cytology in competent and experienced hands is a valuable diagnostic method.

Needle Biopsy

Although needle biopsy has been used with some success in the detection of malignant tumor involving the pleura (24, 25), its reliability in the specific diagnosis of mesothelioma has not been well documented. Our experience is that only rarely does it permit a definite diagnosis. To a greater extent than with most tumors histopathologic assessment depends on the extent of tissue sampling and in needle biopsies this is necessarily limited. The success rate with cytology has been higher than with needle biopsy and the latter would appear to be adjunctive to the former in the demonstration of neoplastic processes in the pleura in general, and in the specific diagnosis of mesothelioma in particular.

Thoracoscopy and Peritoneoscopy

These techniques, which have enjoyed only a limited popularity in the United States, may come into greater use as an alternative to exploratory surgery, especially with the availability of fiberoptic instruments (26–28). Though we are familiar with only one reference to the diagnosis of diffuse mesothelioma made by this means, accurate discrimination in a high proportion of other types of pleural and peritoneal disease has been possible and has saved patients from exploratory surgery. This approach would seem well suited to the diagnosis of mesothelioma, provided that a cavity is still present, since it allows both extensive inspection and guided multiple biopsies.

Exploratory Surgery

By the time a diffuse mesothelioma produces symptoms, physical signs and radiological findings, it is advanced and regarded as beyond the scope of curative surgery (although Butchart et al (29) have very recently proposed pleuropneumonectomy in selected cases).

A limited approach employing the methods mentioned above may yield a diagnosis of probable mesothelioma or at least of malignant process and, in the absence of specific therapy, the clinician may elect to cease further investigation (30). However, at present thoracotomy or laparotomy appear to be performed in the majority of cases, usually for diagnosis, on occasion for relief of distressing symptoms such as are caused by pleural effusion, pulmonary compression by tumor or intestinal obstruction. A thoracotomy may be limited, sufficient for an adequate tissue sampling but providing little gross pathological information. A true exploratory thoracotomy will yield gross pathologic data but clinical considerations will have to justify the procedure.

If laparotomy is performed, in addition to obtaining a gross delineation of the process and biopsy, a primary visceral tumor should be excluded as far as possible. Biopsy is usually taken only from the omentum but if tissue can be sampled from several sites, without increasing the operative risk, it would at times permit more definite pathological diagnosis.

Gross Pathology

The demonstration of diffuse pleural involvement by tumor from apex to diaphragm, with or without evidence of extension into contiguous structures, and in the absence of an apparent primary pulmonary carcinoma, may prove strong supportive evidence of mesothelioma (6, 9, 31, 32, 33, 34). Occasionally in the early stage the tumor appears localized but attempted excision is followed by recurrence and dissemination (34). In the peritoneal cavity the appearance is often indistinguishable from extensive carcinomatosis (16) but here again its diffusely thickened nodular or plaque-like character, occasionally with massive local accumulations, is an important characteristic in the establishment of the diagnosis.

Microscopic Pathology

The microscopic features of diffuse mesothelioma have been well described in a number of the references given above. Suffice it to say here that they range from highly characteristic, patterned pure epithelial and mixed epithelial and mesenchymal types, through sheet-like regular and perhaps differentiated but not specific epithelial and sarcomatoid appearances to anaplastic and even pleomorphic forms. Even in an individual case there may be great differences in sections from various areas.

It has been our experience that these characteristics of mesothelioma result in a not insignificant observer variation even at a high level of expertise (7, 35).

Other Tumors to be Differentiated from Mesothelioma

Since the histologic spectrum of mesothelioma is so broad a variety of carcinomas and sarcomas involving the serous surfaces extensively may simulate mesothelioma to a greater or lesser degree. These are only occasional occurrences in individual experience and there does not appear to have been a systematic study of the problem. Although it constitutes one of the chief concerns of mesothelioma panels, this aspect of their activities has not been reported.

Peripheral pulmonary adenocarcinoma is the best documented imitator of pleural mesothelioma (36, 37). In the peritoneum in women an occasional problem is the differentiation from papillary serous adenocarcinoma of the ovary (38). In rare instances tumors of this type are found where the ovaries are believed not to be the site of origin. The hypothesis of extra-ovarian müllerian tissue as a source has been raised and is discussed elsewhere (39).

Other tumors known to have involved the pleura deceptively, on gross, or microscopic study or both, are thymoma (40), renal cell carcinoma (41) and thyroid carcinoma (31). In the peritoneum occult gastric carcinoma has masqueraded both grossly and microscopically as mesothelioma (42). Other carcinomas involving the serous surfaces extensively can usually be distinguished histologically from mesothelioma with histochemical assistance.

Certain spindle cell or anaplastic tumors of mesenchymal character are sometimes difficult to separate from mesothelioma. Fibrosarcoma, schwannoma and fibrous histiocytoma often suggest themselves in this context. The presence of a large mass in addition to diffuse nodulation, or the history of previous surgery, may provide the clue to distinction.

The presence of a known apparently second independent primary tumor in a case of mesothelioma requires that more than the usual rigor be observed in evaluation. However the distinction is often quite apparent on histologic or histochemical grounds and does not necessarily invalidate the diagnosis of mesothelioma.

Mesothelial Hyperplasia and Desmoplasia

There are cases of subacute or chronic pleuritis and peritonitis of various etiologies where a proliferation of mesothelium and/or fibroblasts raises the possibility of mesothelioma (43). Conversely certain mesotheliomas are so well differentiated, particularly at an early stage in their evolution, that they can be mistaken for reactions to inflammation. The presence of a profuse inflammatory infiltrate favors a reactive process but significant lymphocytic aggregations can be seen in mesothelioma. Collagen increasing with time may obscure the neoplastic character is some mesotheliomas.

Histochemistry for Mucosubstances

These techniques can prove of decisive significance. Unequivocal positivity for epithelial (neutral) mucosubstance is held to exclude mesothelioma (44). However judgment must be based not only on the color reaction but also on the morphology of the positive materials, i.e., its presence as numerous intracytoplasmic vacuoles or globules, as a diffuse coarse granular cytoplasmic staining, or as coagulated secretion within lumina—in short, those characteristics of secretion as seen in adenocarcinoma. Strands of stroma, material within macrophages, scant minute cytoplasmic granules and necrotic matter must be excluded. We have found the PAS reaction after diastase (DPAS) more reliable than mucicarmine when such reservations are observed.

The stain for acid mucosubstance (alcian blue or Hale's colloidal iron) is helpful and occasionally critical, in a smaller number of cases. The presence of positive material in cytoplasmic vacuoles, tubular lumina or spaces within epithelial clusters, where DPAS is negative, is weighty evidence in favor of mesothelioma. If this material is removed by hyaluronidase in whole or in significant part, the diagnosis of mesothelioma is confirmed. Diffuse cytoplasmic staining or a rare positive vacuole is nondiagnostic. Stromal staining is not relevant and similarly the method has no significance with mesenchymal tumors. Although well-differentiated mesotheliomas are more likely to produce hyaluronic acid, a poorly differentiated tumor may show a rare field containing characteristic positive material which is sufficient to resolve doubt.

Ultrastructure

Electron microscopic studies of mesothelioma have been in substantial agreement with light microscopy in demonstrating cells with definitely epithelial characteristics, cells indistinguishable from fibroblasts and apparent intermediate forms (45, 46). Tumors that appear to be mesenchymal by light microscopy may be shown by electron microscopy to contain cells with epithelial characteristics (47). Undoubtedly the nature of some cases not definitely diagnosible at the light microscopic level will be elucidated by electron microscopy. To what extent this is true is not yet certain. It is probable that even this added dimension will not per se permit the definite categorization of all cases.

The Role of the Autopsy in Diagnosis

The autopsy, once regarded by many as essential for the definite diagnosis of mesothelioma (48), is now generally held to bear the same relationship in the identification of that tumor as with other tumors (31, 49). That is, where sufficient information has not been obtained during life for diagnostic conviction an autopsy may be determinative. Exclusion of another primary site is still an important element in the diagnosis of mesothelioma but positive evidence in the categories discussed above is more essential. An autopsy is the most convincing of exclusionary procedures and permits the most comprehensive evaluation of positive aspects of the gross pathology as well as a wide sampling of tumor for histologic study. Invasion and metastasis can be delineated. However, an autopsy has its qualifications. Technical difficulties with very extensive tumor involvement, the necessity for painstaking thoroughness in the performance of dissection and the need for experienced judgment in interpretation increase the possibility of erroneous diagnosis. The oversight of an occult primary tumor is a well-known hazard. Even when the gross findings are apparently concordant the diagnosis of mesothelioma cannot be accepted if the histology is not consistent.

Evaluation of Parameters of Diagnosis and the Statement of Diagnosis

The elements of diagnosis of mesothelioma may be listed in order of logical consideration and of weight as follows:

1. Microscopic morphology. Fluid cytology, histochemistry, fluid chemistry and ultrastructure as adjuncts.
2. Gross morphology. Autopsy or exploratory surgery.
3. Studies exclusionary of another primary source. Autopsy, exploratory surgery, radiographic and radioisotopic procedures, endoscopic and physical examination.
4. History and other clinical aspects.

Item 1 when characteristic, especially if strengthened by the adjunctive procedures, could yield a highly probable diagnosis. An experienced observer might develop conviction sufficient for a definite diagnosis without any other data. With supportive information as in item 2, or elements of items 3 and 4, in a histologically characteristic case a definite diagnosis is readily established.

If the microscopic appearance is nonspecific, support by items 2 or 3 would be required for definite conclusion, otherwise one could say no more than that the case was probably or only possibly a mesothelioma. With increasing departure from a characteristic cytohistology and increasing anaplasia strongly confirmatory information developed under 2, 3 and 4 would be required. However no matter how concordant the facts under 2, 3 and 4, they should not lead to a grading as definite if the neoplasm is very noncharacteristic microscopically or undifferentiated. Here the diagnosis must be qualified as probable at most. Conversely even with a relatively persuasive histology, marked deviation from typical features under 2 or 3 should make for caution in diagnosis.

The need for calculation of the degree of certainty of diagnosis has been implied or stated by a number of authors (7, 36, 43, 48, 50). Terms such as definite, typical, probable, possible, unlikely, or doubtful have been frequently employed. A numerical system graded from 0, not a mesothelioma, to 4, definitely a mesothelioma, has been useful for Mesothelioma Panel purposes and statistical studies (7, 35). In hospital practice for communication to a clinician and for record, terms such as definite, probable or possible, perhaps further qualified to suite the individual situation, are desirable, if not requisite, to convey the complexity, and in many cases limitations, of the decision indicated. Much of this is already standard practice in dealing with atypical, complex and undifferentiated tumors in general.

It is hoped that such qualifications in relation to mesothelioma would carry into tumor registries and the reporting of cases for national epidemiological purposes. This, along with more reliable diagnosis in general, would do much for the assessment of the seriousness of the mesothelioma problem.

References

1. Wagner, J. C., Sleggs, C. A., and Marchand, P.: Diffuse Pleural Mesothelioma and Asbestos Exposure in the North Western Cape Province, Brit J Industr Med 17:260–271, 1960.
2. Selikoff, I. J., Churg, J. and Hammond, E. C.: Asbestos Exposure and Neoplasia, JAMA 188:22–26, 1964.
3. Newhouse, M. L. and Thompson, H.: Mesothelioma of Pleura and Peritoneum Following Exposure to Asbestos in the London Area, Brit J Industr Med 22:261–269, 1965.
4. Lieben, J. and Pistawka, H.: Mesothelioma and Asbestos Exposure, Arch Environ Health 14:559–563, 1967.
5. McEwen, J., Finlayson, A., Muir, A., and Gibson, A. A.: Mesothelioma in Scotland, Brit Med J 4:575–578, 1970.
6. Hourihane, D. O'B.: The Pathology of Mesotheliomata and an Analysis of Their Association with Asbestos Exposure, Thorax 19:268–278, 1964.
7. McDonald, A. D., Magner, D., and Eyssen, G.: Primary Malignant Mesothelial Tumors in Canada, 1960–1968, Cancer 31:869–876, 1973.
8. Greenberg, M. and Lloyd Davies, T. A.: Mesothelioma Register 1967–1968, Brit J Industr Med 31:91–104, 1974.
9. Thomson, J. G.: The Pathological Diagnosis of Mesothelioma of the Pleura and Peritoneum. In *Proceedings of the International Conference on Pneumoconiosis,* Shapiro, H. A. (Ed). Oxford University Press, Capetown 1970, p. 150.
10. Newhouse, M. L. and Wagner, J. C.: Validation of Death Certificates in Asbestos Workers, Brit J Ind Med 26:302–307, 1969.
11. Ratzer, E. M., Pool, J. L., and Melamed, M. R.: Pleural Mesotheliomas. Clinical Experience with 37 Patients, Amer J Radiol 99:863–880, 1967.
12. Oels, H. C., Harrison, E. G., Carr, D. T. and Bernatz, P. E.: Diffuse Malignant Mesothelioma of the Pleura. A Review of 37 Cases, Chest 60:564–570, 1971.
13. Elmes, P. C.: The Natural History of Diffuse Mesothelioma. In *Biological Effects of Asbestos,* Bogovski, P. (Ed). Lyon, International Agency for Research on Cancer, 1973, p. 267.
14. Roberts, G. H., and Irvine, P. N.: Peritoneal Mesothelioma. A Report of 4 Cases, Brit J Surg 57:645–650, 1970.
15. Moertel, C. G.: Peritoneal Mesothelioma, Gastroenterology 62:346–350, 1972.
16. Kannerstein, M., and Churg, J.: Peritoneal Mesothelioma, Human Pathol. 8:83–94, 1977.
17. Harington, C. S., Wagner, J. C., and Smith, M.: The Detection of Hyaluronic Acid in Pleural Fluids of Cases with Diffuse Pleural Mesotheliomas, Brit J Exper Med 44:81–83, 1963.
18. Castor, C. W., and Naylor, B.: Acid Mucopolysaccharide Composition of Pleural Effusions, Cancer 20:462–466, 1967.
19. Boersma, A., Degand, P. and Havez, R.: Diffuse Mesothelioma: Biochemical Stages in the Diagnosis, Detection and Measurement of Hyaluronic Acid in Pleural Fluid. In *Biological Effects of Asbestos,* Bogovski, P. (ed.). International Agency for Research on Cancer, Lyon, 1973, p. 65.

20. Klempman, S.: The Exfoliative Cytology of Diffuse Pleural Mesothelioma, Cancer 15:691-695, 1962.
21. Naylor, B.: The Role of the Cytology Laboratory in the Diagnosis of Diffuse Malignant Mesothelioma. In *Transactions of International Conference on the Biological Effects of Asbestos*, Dresden, 1968, p. 288.
22. Butler, S. B., and Berry, A. V.: Diffuse Mesothelioma. Diagnostic Criteria using Exfoliative Cytology. In *Biological Effects of Asbestos*, Bogovski, P. (Ed). International Agency for Research on Cancer, Lyon, 1973, p. 68.
23. Roberts, G. H. and Campbell, G. M.: Exfoliative Cytology of Diffuse Mesothelioma, J Clin Path 25:577-782, 1972.
24. Salyer, W. R., Eggleston, J. C., and Erozan, Y. S.: Efficacy of Pleural Needle Biopsy and Pleural Fluid Cytology in the Diagnosis of Malignant Neoplasm Involving the Pleura, Chest 67:536-539, 1975.
25. Von Hoff, D. D., and LiVolsi, V.: Diagnostic Reliability of Needle Biopsy of the Parietal Pleura, Amer J Clin Path 64:200-204, 1975.
26. DeCamp, P. T., Mosley, P. W., Scott, M. L., and Hurst, H. B., Jr.: Diagnostic Thoracoscopy, Ann Thoracic Surg 16:79-84, 1973.
27. Senno, A., McAllem, F., Quijano, E., Tan, B., and Klauss, R.: Fiberoptic Thoracoscopy, NY State J Med 75:51-54, 1975.
28. Rivera, R. A., and Bryce, H. W.: Peritoneoscopy: Analysis of 150 Cases, Amer J Gastroenterol 58:584-601, 1972.
29. Butchart, E. G., Ashcroft, T., Barnsely, W. C., and Holden, M. P.: Pleuropneumonectomy in the Management of Diffuse Malignant Mesothelioma of the Pleura. Thorax 31:15-24, 1976.
30. Elmes, P. C.: Therapeutic Openings in the Treatment of Mesothelioma. In *Biological Effects of Asbestos*, Bogovski, P. (Ed). International Agency for Research on Cancer, Lyon, 1973, p. 277.
31. McCaughey W. T. E.: Criteria for the Diagnosis of Diffuse Mesothelial Tumors, Ann NY Acad Sci 132:603-613, 1965.
32. Churg, J., Rosen, S. H., and Moolten, S. E.: Histological Characteristics of Mesothelioma Associated with Asbestos, Ann NY Acad Sci 132:614-622, 1965.
33. Whitwell, F., and Rawcliffe, R. M.: Diffuse Malignant Mesothelioma and Asbestos Exposure, Thorax 26:6-22, 1971.
34. Churg, J., and Selikoff, I. J.: Geographic Pathology of Pleural Mesothelioma. In *The Lung*, Liebow, A. A. (Ed). Williams and Wilkins Co., Baltimore, 1967, p. 284.
35. McCaughey, W. T. E., and Oldham, P. D.: Diffuse Mesothelioma: Observer Variation in Histological Diagnosis. In *Biological Effects of Asbestos*, Bogovski, P. (Ed). International Agency for Research on Cancer, Lyon, 1973, p. 58.
36. Webster, I.: Mesotheliomatous Tumors in South Africa, Ann NY Acad Sci 132:623-646, 1965.
37. Harwood, T. R., Gracey, F. R., and Yokoo, H.: Pseudomesotheliomatous Carcinoma of the Lung: A Variant of Peripheral Lung Cancer, Amer J Clin Path 65:159-167, 1976.
38. Ackerman, L. V.: Tumors of the Retroperitoneum, Mesentery and Peritoneum, In *Fascicle 23, Atlas of Tumor Pathology*. Armed Forces Institute of Pathology, Washington, D.C., 1954, pp. 101, 109.
39. Kannerstein, M., Churg, J., McCaughey, W. T. E., and Hill, D. P.: Papillary Tumors of the Peritoneum in Women: Mesothelioma or Papillary Carcinoma, Am J Obstet Gynecol 127:306-314, 1977.
40. Payne, C. B., Jr., Morningstar, A. A. and Chester, E. H.: Thymoma of the Pleura Masquerading as Diffuse Mesothelioma, Am Rev Resp Dis 94:441-446, 1966.
41. Unpublished case.
42. Schepers, G. W. H.: Discussion, Ann NY Acad Sci 132:599, 1965.
43. Hourihane, D. O'B.: A Biopsy Series of Mesotheliomata and Attempts to Identify Asbestos within Some of the Tumors, Ann NY Acad Sci 132:647-673, 1965.
44. Kannerstein, M., Churg, J. and Magner, D.: Histochemistry in the Diagnosis of Mesothelioma, Ann Clin Lab Sci 3:207-211, 1973.

45. Wang, N. S.: Electron Microscopy in the Diagnosis of Pleural Mesothelioma, Cancer 31:1046–1054, 1973.
46. Suzuki, Y., Churg, J., and Kannerstein, M.: Ultrastructure of Human Malignant Diffuse Mesothelioma, Amer J Path 85:241–262, 1976.
47. Kay, S., and Silverberg, S. G.: Ultrastructural Studies of a Malignant Fibrous Mesothelioma of the Pleura, Arch Path 92:449–455, 1971.
48. Report and Recommendations of the Working Group on Asbestos and Cancer, Ann NY Acad Sci 132:717, 1965.
49. Bolio-Cicero, A., Aguirre, J., and Perez-Tamayo, R.: Malignant Peritoneal Mesothelioma, Amer J Clin Path 36:417–426, 1961.
50. Huguenin-Dumittan, S. A.: Les Mesothelioma Pleuraux, Schweiz Med Wschr 98:215–227, 1968.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

Sexual Aspects of the Female Diabetic

MAX ELLENBERG, M.D.

Abstract

There is little available data on the sexual aspects of the female diabetic although there is a recognized increased incidence of impotence in the male diabetic primarily attributable to pelvic autonomic neuropathy. Since the female diabetic is at equal risk for the development of pelvic autonomic neuropathy, it has been assumed that there is an equal effect of diabetes on female sex activity. To investigate this, 54 diabetics with neuropathy were evaluated with regard to libido and orgasmic response. As a control group, 46 female diabetics without neuropathy were studied in similar fashion. The ages of both groups were comparable ranging from 24 to 73 years; duration of diabetes was equally comparable and ranged from 1 to 53 years.

The results indicate that there was no diminution in libido or fulfillment of the sex drive in either group as compared with the nondiabetic female population. Not only was there no effect of neurologic complications on sex performance in the female, including neurogenic bladder, Charcot joints, neuropathic ulcer, diabetic diarrhea, etc. Other serious complications such as blindness, retinopathy and nephropathy had no impact. The difference between the two sexes cannot be explained on anatomical, neurologic, or physiologic grounds. An obvious difficulty is the lack of any objective measurement in the female and therefore the need to rely on the patient's statement. These observations may reflect psychological factors in female sexuality.

There is little known or documented about the effects of diabetes on female sexuality. This is surprising since the deleterious effects on sex performance in the male diabetic have been long recognized. A considerable portion of this increased impotence is attributable to pelvic autonomic neuropathy (1). Since the female is at equal risk for the development of diabetic neuropathy with involvement of the pelvic autonomic nervous system, one would postulate a comparable impairment of sex function.

The purpose of this study was to evaluate sexuality in the female diabetic. Fifty-four consecutive female diabetic patients with clinically demonstrable neuropathy were investigated. The presence of neuropathy was established by absent deep reflexes, particularly the ankle jerks, and sensory impairment in the feet and toes. They were questioned as to their interest in sex and the presence or absence of orgasmic reaction. As a control, forty-six female diabetic patients without demonstrable clinical neuropathy were selected to match age and duration of diabetes. The controls were questioned in identical fashion as to their sex interest and performance. There was a total of 100 patients. As seen in Table I the ages of the patients varied from 20 to 70 years with the majority of patients being in the 30 to 60 year age group. The duration of diabetes was more than 10 years for the vast majority and over 20

From the Department of Medicine, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Max Ellenberg, M.D., 936 Fifth Avenue, New York, N. Y. 10021.

years in more than half. One of the patients with neuropathy had insulin-dependent diabetes for fifty-three years. It is also apparent that the two groups are comparable in age and duration of diabetes.

The results are shown in Table II. The facts are evident: 1) there is no difference between those with and those without neuropathy: 2) even more startling is the lack of effect of diabetes on sex performance. Specifically 44 of the 54 patients with neuropathy and 38 of the 48 without neuropathy had libido and orgasmic reaction. This compares most favorably with the statistics for female sexuality in the nondiabetic population (2). Seven of the 54 with neuropathy had diminution of libido and orgasm and only 3 reported absence of libido and orgasm. The same relative percentages apply to those without neuropathy. Strikingly, the comparable classic picture of sex involvement in the diabetic male, namely, retention of libido and absence of potency, is not present in these 100 female diabetics, i.e., none reported persistence of libido with loss of orgasmic reaction.

As seen in Table III the neuropathic complications of the 54 women with diabetic neuropathy run the entire gamut. In addition to peripheral neuropathy which they all had, many also had neurogenic vesical dysfunction, neuropathic ulcers, Charcot joints, neuropathy involving all the elements of the gastrointestinal tract such as gastropathy, esophogeal neuropathy and diabetic diarrhea, dropped foot, oculomotor paralysis, and mononeuropathy multiplex. This is especially noteworthy since many of these neuropathic complications are associated with impotence in the male diabetic. In addition, other complications such as blindness, severe retinopathy, nephropathy including significant azotemia, peripheral vascular disease, angina, and severe necrobiosis lipoidica diabeticorum had no measurable effect on sexual performance in the female diabetic.

Several cases of unusual interest are worthy of mention. One patient had

TABLE I

	Duration of diabetes					
	0–10	10–20	20–30	30–40	40–50	>50
Neuropathy	12	12	16	9	4	1
No Neuropathy	11	11	16	5	3	
	Age of patients					
	29–30	30–40	40–50	50–60	60–70	>70
Neuropathy	10	18	13	10	2	1
No Neuropathy	11	14	12	8	1	

TABLE II

Libido	Orgasm	Neuropathy (54)	No neuropathy (48)
+	+	44	38
↓	↓	7	6
–	–	3	2
+	–	0	0

TABLE III

Neuropathic Complications

Diabetic Neuropathy – 54
Neuropathic Ulcer – 5
Neuropathic (Charcot) Arthropathy – 9
Esophageal Neuropathy – 2
Gastropathy – 2
Enteropathy – 4
Neurogenic Bladder – 7
Dropped Foot – 2
E.O.M. Paralysis – 4
Mononeuritis Multiplex – 3

Other Complications

Retinopathy – 36
Blindness – 5
Nephropathy – 18
Papillary Necrosis – 2
Dupuytren's Contracture – 3
Angina – 2
Necrobiosis Lipoidica Diabeticorum – 3
Gout – 2

had a normal sex life with normal libido and orgasmic response until she developed an episode of severe painful neuropathy. During the course of the syndrome which lasted about a year, her interest in sex disappeared. However, as the symptoms of the neuropathy regressed her interest in sex returned and now she is enjoying sex again and having normal orgasmic reaction. One patient, a virgo intacta, reported the ability to obtain orgasmic reaction when masturbating accompanied by appropriate vaginal secretion; this patient has Charcot's joints, gastropathy and enteropathy. One of the patients who has had painful neuropathy and now has esophageal neuropathy, gastropathy, diarrhea, cataracts, marked bladder involvement, nephropathy, retinopathy, and neuropathic ulcer states that she indulges in sex, enjoys it, and has orgasmic reaction. Another patient with neurogenic bladder and superimposed renal papillary necrosis accompanied by azotemia and blindness still enjoys sex; she has had two pregnancies both of which ended with miscarriages at seven months. Another, aged 40 has had diabetes for thirty years; although there is retinopathy, neuropathy and Dupuytren's contracture, she has two children and enjoys daily intercourse. The patient with the longest duration of diabetes in this series namely, fifty-three years of insulin-dependent diabetes, has normal sex drive and normal orgasmic reaction.

How does one explain this remarkable difference in sex function between male and female diabetics? An obvious difficulty is the lack of any objective measurement of sexual response in the female and therefore the need to rely entirely on the patient's statement. One possibility is that we are dealing with a peculiar nonrepresentative group of patients. This is unlikely since these females were taken from the same practice where a 60% occurrence of impotence was noted in the diabetic male (1). Further, in two other studies the absence of any relationship of diabetes on female sexuality was noted (3, 4). Although one report found 35% of 125 diabetic women to be nonorgasmic, it is significant that there was no correlation of diabetic female sexual function with age, duration, insulin dose, or such complications as neuropathy, retinopathy or nephropathy (5).

The possibility of anatomical differences was investigated to try to shed some light on the findings. As seen in Table IV, the anatomical homologues, all of which derive from identical embryonal anlage, are entirely comparable. Specifically, the penis is homologous with the clitoris, the integument of the shaft of the penis with the labia minora and the integument of the scrotum with the labia majora. Thus there is no discernible anatomical evidence to account for the observations.

The neurologic innervations were then compared for any significant differences. As seen in Table V, the spinal centers of reflex control of the sex organs in male and female are similar. In addition the involved afferent and efferent nerves of the autonomic as well as of the voluntary system entirely correspond. And finally the response to tactile stimulation is identical in both sexes.

The next area of possible explanation was physiologic relationship. This

TABLE IV

Anatomical Homologues

Male	Female
Penis	Clitoris
Corpora cavernosa and spongiosum	Erectile tissue
Integument of shaft of penis	Labia Minora
Integument of scrotum	Labia Majora

TABLE V

Neurological Innervation

	Male	Female
Spinal centers of reflex control of sex organs	Identical	
Afferent and efferent nerves involved		
a) autonomic	Identical	
b) voluntary	Identical	
Response to tactile stimulation	Identical	

TABLE VI

Physiological Relationships

Male	Female
Erection	Turgor of the erectile tissue in the clitoris
Discharge of seminal fluid	Discharge of secretion of Bartholin's glands

Sexual orgasm identical except female has no ejaculation.

could be significant since it represents the direct mechanism of orgasmic reaction. As noted in Table VI erection in the male is identical with turgidity of the erectile tissue in the clitoris and the discharge of seminal fluid is entirely analogous to the discharge of secretion of Bartholin's glands. Sexual orgasm is alike in all respects in both sexes with the exception of the fact that the female has no ejaculation.

Thus there is no basis to explain the observed sexual differences on anatomy, neurology, or physiology. As already indicated one difficulty is the lack of any objective measurement of female sex activity and the need to rely entirely on the patient's statement. One explanation may lie in the psychological aspect of sexual behavior. There are many observations that would tend to support this possibility. The entire body is involved whenever there is any sexual responsiveness. There is some tendency lately to become overly preoccupied with the physiology of sexuality and to forget that a sexual encounter in human terms is a much more complicated phenomenon than mere spinal reflex activity. A brain and a cord are necessary for the human animal to recognize sexual satisfaction. The central nervous system exerts its control, facilitating and inhibiting responses, while also adding its own special ingredients, namely fantasy, expectations, memories, and emotional situations. The case of the human paraplegic affords a clue in that genital stimulation will result in erection but there is no awareness of the physiologic changes by the patient. He is not conscious of sexual satisfaction when he has coitus even though he may attain an erection and achieve actual orgasm. Remarkably, however, some paraplegics have orgasmic imagery in dreams almost as vividly as if it were the real thing. Thus, cognitional eroticism can be a variable of sex entirely independent of genito-pelvic sensation and action. In other words, the brain can work independently of the genitalia in the generation of erotic experience just as the genitalia of paraplegics can work reflexively and independently of the brain. Signals other than from the genito-pelvic area become competent to release erotic response.

Masters and Johnson (6) in their definition of orgasm stress the psychophysiologic components. Physiologically it is a brief episode of physical release; psychologically it is a subjective perception of a peak of reaction of sexual stimulus. Ultimately orgasm is an intensely subjective experience in the female and is perhaps best conceptualized as a peak experience and an acutely pleasurable moment. Specific physiological responses are not necessary for sexual satisfaction.

In contrast to the factors that stimulate the male partner, which are to a large extent the physical attractiveness of the woman, the emotional attitude toward the man is of greater importance for the response of the woman. Tenderness and the security provided by the feeling of being loved are necessary requirements for the woman's response. Stated differently, the sex drive in man is primarily physical, whereas sexuality in the female encompasses a higher psychological and emotional level.

Further investigation is indicated to clarify the significance of these observations. One of the first goals is to develop an objective measurement of female sexual responsiveness.

References

1. Ellenberg, M.: Impotence in Diabetes: The Neurologic Factor, Ann Int Med 75:213, 1971.
2. Kinsey, A. C., Pomeroy, W. B., Martin, C. F., and Bebhard, P. H.: *Sexual Behavior in the Human Female*. W. R. Saunders & Co. Philadelphia 1953.
3. Roque, J. L.: Personal communication.
4. Dock, W.: Personal communication.
5. Kolodny, R. C.: Sexual Dysfunction in Diabetic Females, Diabetes 20:557, 1971.
6. Masters, W. H. and Johnson, V. E.: *Human Sexual Response*. Little, Brown & Co., Boston, 1966.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

Convergence Spasm

PETER HERMAN, M.D.

Spasm of convergence of an organic nature is a rarely encountered condition (1, 2). Perusal of the literature disclosed fewer than ten cases on record, none having come to autopsy. Patient 1 is the first case in which electrooculography was performed. Patient 2, with convergence spasm of hysterical origin, is the first in which sodium amobarbital was successfully used to stop the ocular signs. A brief review of the literature, an outline of the differential diagnostic problems, along with remarks for treatment complete the report.

Case Reports

Patient No. 1. The first patient, a 58-year-old chronic alcoholic male was admitted inebriated to the hospital.

Examination: Blood pressure 130/80, pulse 80, and temperature 98°F. He had occasional outbursts of rage, was disoriented as to time and place, and could not name presidents, spell 'cat,' or handle simple arithmetic. His speech was somewhat garbled and he spoke in short explosive sentences.

Direct fundoscopy revealed sheathing of arteries with mild narrowing. The optic discs were pink and the contours sharp. Vision was 20/60-2 and 20/25-2. Fields were full for 2 cm white and red objects.

Intraocular muscles: The pupils were 2 mm (in daylight), irregular, and both reacted very sluggishly to flashlight. Voluntary convergence was good with further pupillary constriction. Duction of separate eyes was full and the patient was able conjugately to move his eyes on command without difficulties in all four gaze directions. He maintained forward vision with apparent orthophoria (Fig. 1). However, on following a target horizontally, his eyes were not continuously "in phase," the abducting eye lagging behind the adductor. This occurred in both

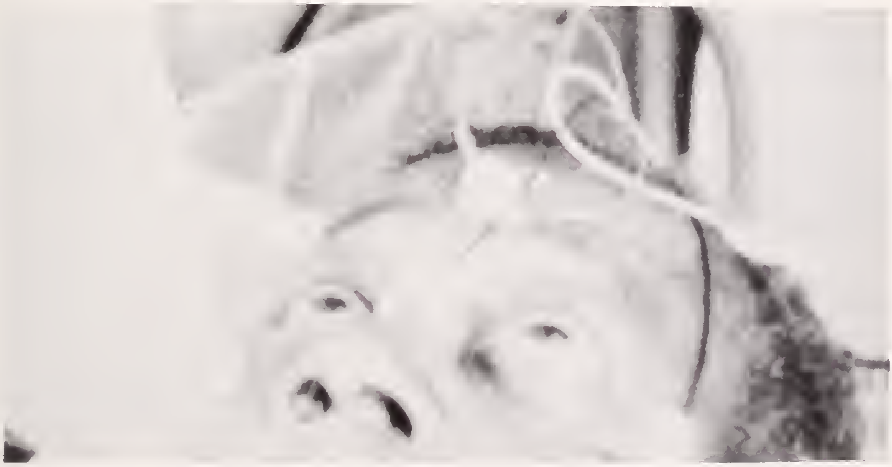

FIG. 1. Case No. 1 looking straight ahead. Note orthophoria.

From the Department of Neurology, The Mount Sinai Hospital, New York, N. Y. 10029.

Requests for reprints should be sent to: Peter Herman, M.D., Mount Sinai Hospital, Atran Building 710, Fifth Avenue and 100 Street, New York, N. Y. 10029

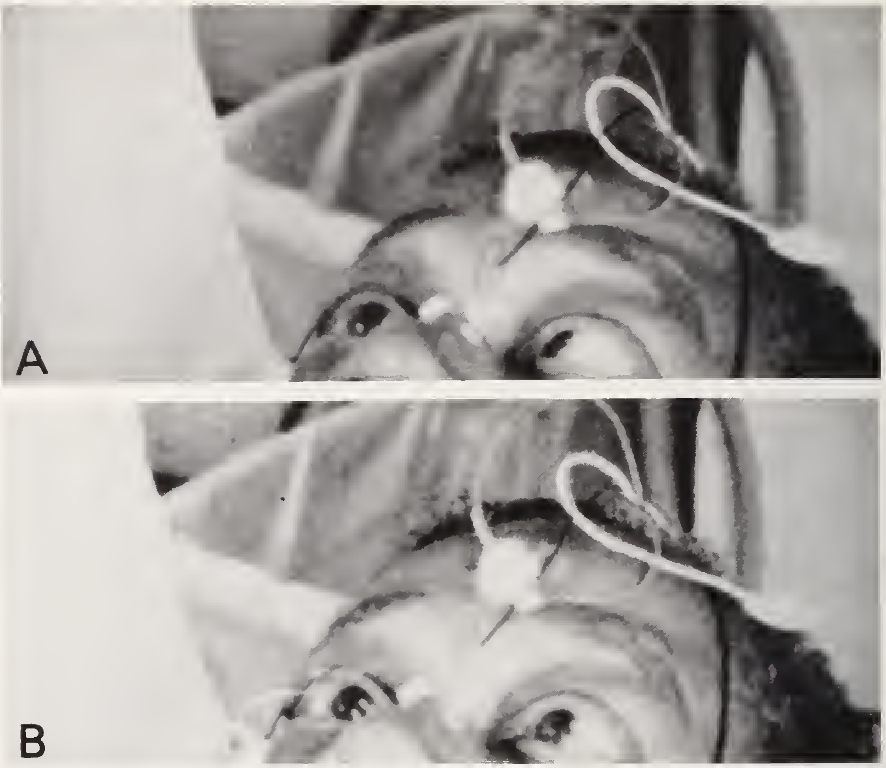

Fig. 2. Case No. 1. Note the movie frames showing the eyes "lagging" in abduction: (A) to the right; (B) to the left; (C) electroocular recording of eyes following a target. First line – left eye. Second line – right eye. The abducting eye lags behind the adducting eye.

gaze directions (see EOG* and Figs. 2A, B, and C). After a few following movements, the excursion of the abducting eye became increasingly limited, resulting in the eyes performing short sweeps, finally becoming locked in a forceful convergent spasm associated with miosis and lasting for several seconds (see EOG and picture frame, Figs. 3A and 3B).

When first seen, the spontaneous paroxysm of convergence could be easily elicited and lasted for five to six seconds, but by the time the patient's eye movements were recorded four weeks later, the convergence spasm was difficult to elicit and of shorter duration.

The patient never had nystagmus and OKN was present in all gaze directions. Passive head turning of the head produced full deviation of the eyes. The Bell's phenomenon was intact.

The remainder of the cranial nerve examination was normal. Motor examination showed full power in all four limbs. Sensory examination showed quick withdrawal to pinprick throughout. Vibration could not be tested. Position sense was decreased in lower extremities but intact in upper extremities. Finger to nose was well performed but heel to shin was fragmentary and impossible to perform.

Deep tendon reflexes were decreased in upper extremities and absent at the ankle and knee. Plantar responses were flexor. Gait was insecure with short steps and "marche á petit pas," with the patient continuously looking at his feet while walking.

Ancillary data: present EEG and a previous one performed one year earlier were read as normal. Skull x-ray revealed bilateral burr holes. Blood VDRL was weakly reactive, AFT-abs. was nonreactive. Lumbar puncture: normal manometrics, no cells, sugar 65 mg/ml, protein 17

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* Electrooculography.

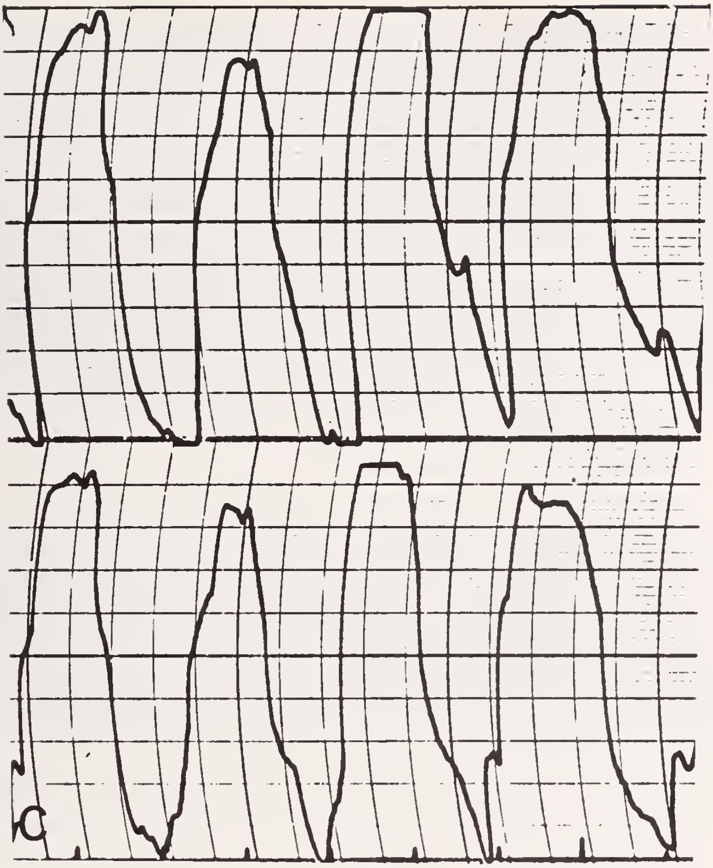

FIG. 2C

mg/ml. Chest x-ray showed fibrocalcific densities in both upper lobes. Sedimentation rate 47. Liver function: increase in transaminase, billirubin, and total protein.

Patient No. 2. A 22-year-old women was admitted on March 26, 1975 for evaluation of eye movements disorder. One month prior to admission she noted a sharp pain in her right temple followed by the feeling that her "eyes were moving the whole day," and that objects were constantly in motion, blurred, and sometimes appeared double. Ten years ago, at age twelve, the patient developed bizarre eye movements that lasted intermittently for two and one-half years. They were diagnosed as hysteria at another institution.

General physical examination was unremarkable. During the first examination, irregular convergence with eye fluttering was observed on attempted upward gaze, while horizontal eye movements induced occasional beats of nystagmus of the abducting eye. Continuous irregular convergence movements during head rotation were observed behind Frenzel glasses (Fig. 4). EOG of spontaneous convergence spasm was performed in light and darkness with no apparent differences. The convergence spasms were the result of irregular converging saccadic movements slower than usually seen in nystagmus. Caloric stimulation induced appropriate but poor nystagmus with persistence of convergence spasm. (Fig. 5). EOG was recorded with IV sodium amobarbital injection. After 300 mg the convergence spasm decreased and the patient was able to perform good conjugate eye movement. OKN was impressively improved (Fig. 6A and B). A second IV sodium amobarbital injection was performed a few days later. After 350 mg., the patient started to have nystagmus on conjugate gaze; thereafter, the eyes moved

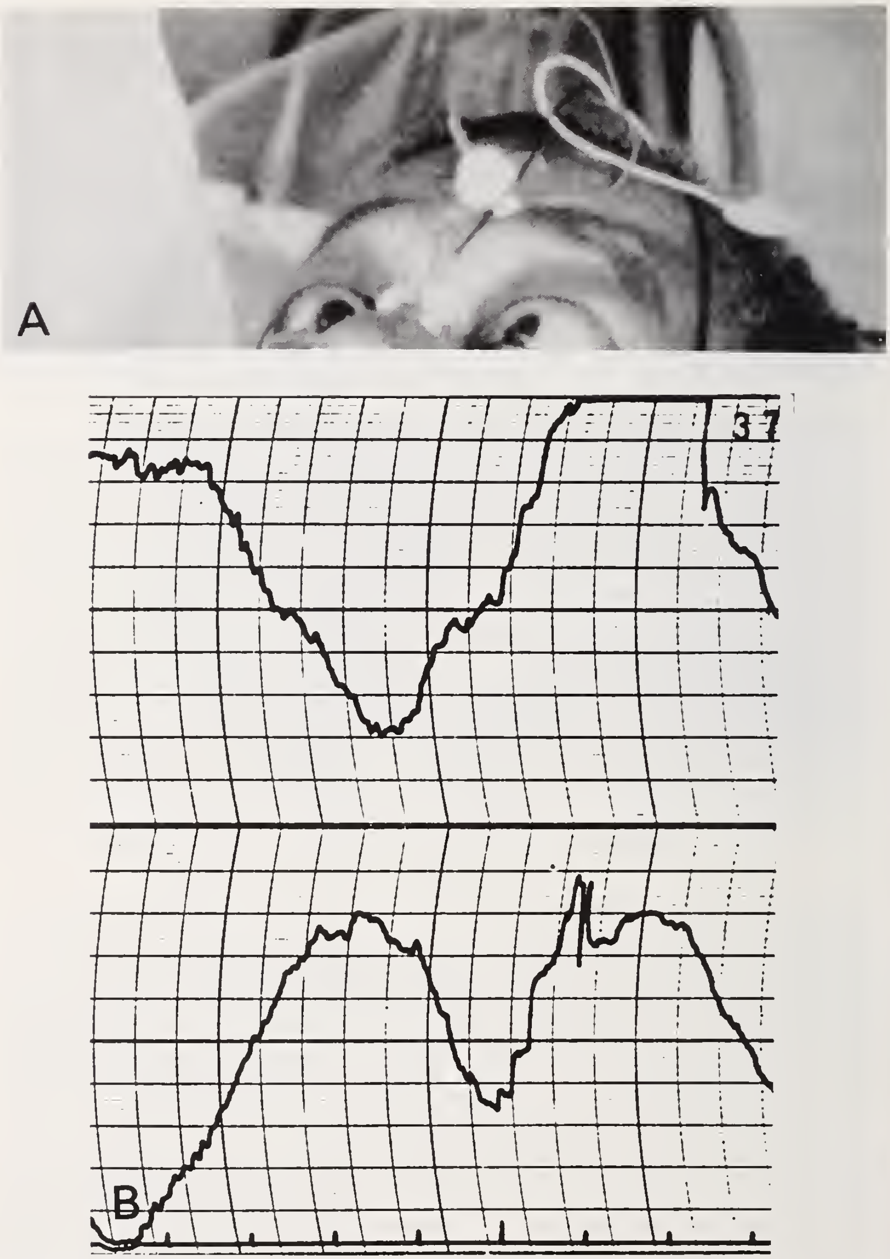

Fig. 3. Case No. 1. (A) forceful convergent spasm following a few right and left pursuit movements movie frames. (B) electroocular recording of the convergence spasm.

conjugately to command and the convergence spasm stopped. At this time, the patient could not perform convergence, even on command, and she reported that the objects "stopped moving around." IV injections of Valium 10 mg five days later had no effect on the convergence spasm that recurred in the meantime. She was started on Thorazine 100 mg/day with initial improve-

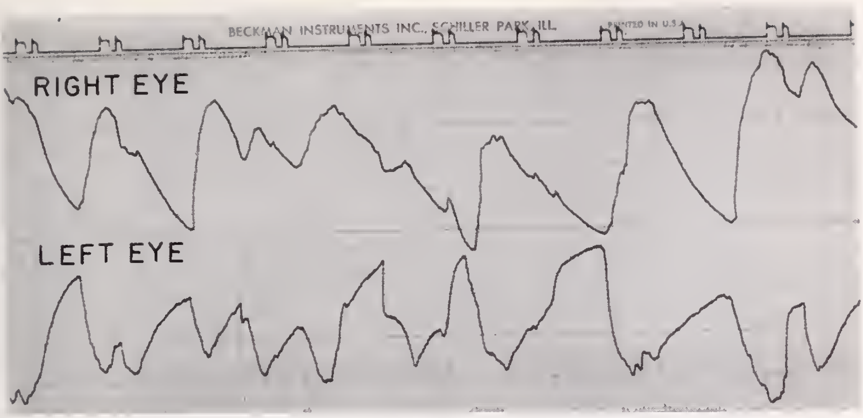

FIG. 4. Case No. 2. Convergence spasm during head rotation.

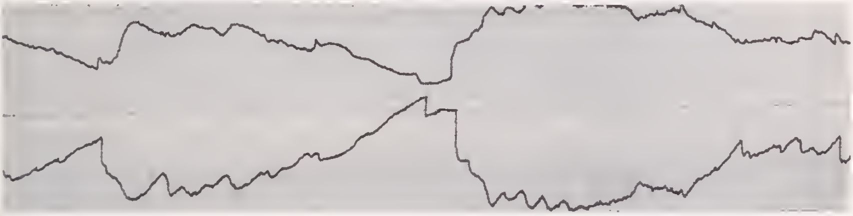

FIG. 5. Case No. 2 Caloric stimulation right ear. Upper trace – right eye. Lower trace – left eye. Note that in spite of calorics the convergence spasm *persists*.

ment in her conjugate gaze, while OKN was intact most of the time. Disconjugate eye movement, occasionally with nystagmus and convergence spasm recurred. Covering of one eye at such times decreased the oscillatory movements of the other eye (the reverse occurs in "latent nystagmus"). The hot bath test was performed with T. at 104.3° F. The patient developed bilateral amblyopia which was thought to be of hysterical type. Other neurologic procedures included spinal tap (with gamma globulin), brain scan and pneumoencephalogram; were all normal. Thorazine doses were at times as high as 600 mg/day without obvious improvements of her ocular movements or changes in her complaints.

Discussion

Convergence spasm (1) is the name interchangeably used for ocular spasm, spasm of accommodation, and spasm of the near reflex. On theoretical grounds, the latter should be favored since it describes the three phenomena occurring simultaneously – namely, convergence, accommodation, and constriction of the pupils. Practically, however, the name convergence spasm has been established by usage. In most large medical centers a few cases of convergence spasm are seen every year, mostly in the Ophthalmology Department, most of these cases being functional in origin and as such, diagnostically and therapeutically frustrating.

In spite of the foregoing, convergence spasm results in rare instances from

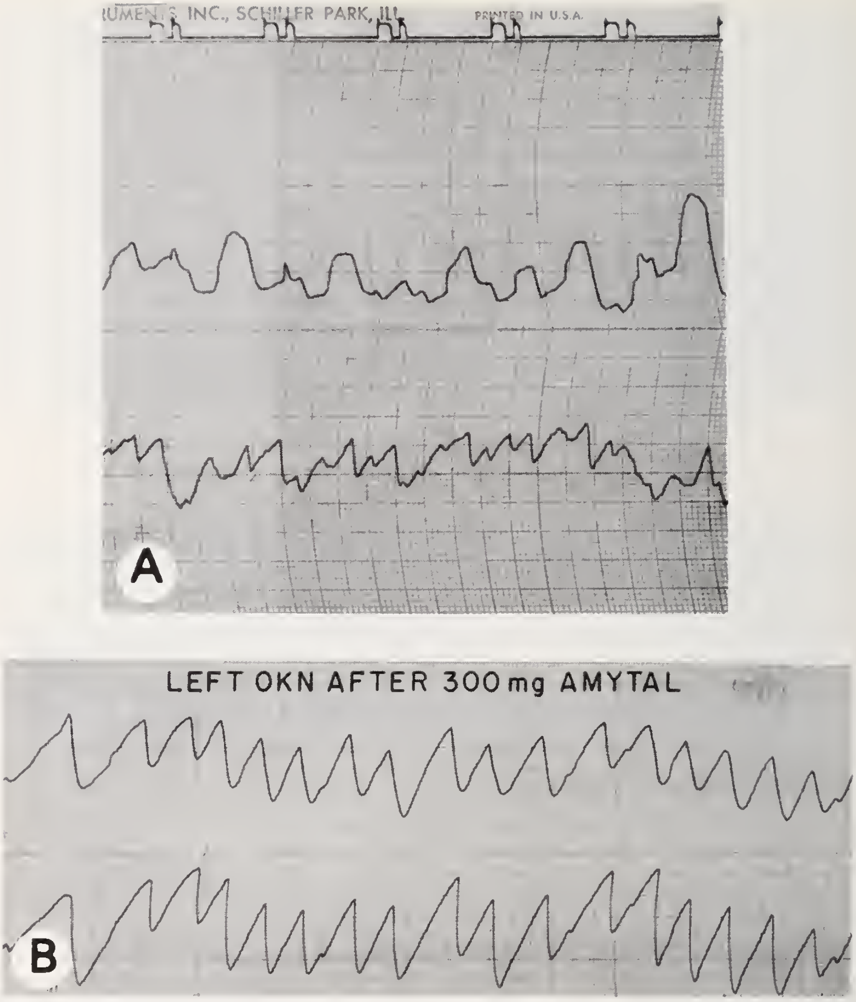

Fig. 6. Case No. 2. EOG recording of OKN. (A) OKN before sodium amobarbital. (B) OKN after sodium amobarbital.

organic affection of the central nervous system (1–6). Curschman (7) in 1906 reported one personal case associated with tabes dorsalis. However, he points out the rarity of this association, none being found in review of 400 cases of tabes compiled from the literature of the epoch. Delbeke and Van Bogaert (8) reported in 1923 a case of convergence spasm becoming manifest there years after encephalitis and quote Houin (9) as describing the same phenomenon in epidemic encephalitis in 1921. DeMorsier and Balavoine (10) reported four cases, three secondary to head trauma and concussion and one secondary to mastoidectomy for evacuation of a cholesteatoma. All their patients had an associated "sensory-motor" syndrome with the spasm occurring while the patient performed an eye movement usually looking toward the side on which weakness of the limbs was present. Kestenbaum (11) mentions it in Parkinson's disease, but Yahr (12), in spite of his large experience with Parkinson's disease, has not seen it (personal communication). Additional cases following trauma or infection of the labyrinth have been reported by various authors (1, 2, 5, 10, 13). Neoplasms rarely cause this syndrome, thus Cogan (1) reported one case associated with a posterior fossa tumor out of his sixteen reported patients with convergence spasm. Kornblueth (14) described in great detail convergence spasm without pupillary constriction occurring on attempted upward gaze in a youngster with pinealoma of the midbrain.

In 1969, Thomson (15) reported the first case of convergence spasm occurring with Wernicke's encephalopathy. Finally, Verbiest (16) observed convergence spasm occurring in myotonic dystrophy.

It is interesting to note here that the first patient's eye dysfunction was apposite to the one seen in bilateral (medial longitudinal fasciculus) MLF syndrome where bilateral adduction is defective (17). Moreover, multiple sclerosis, an entity which has mimicked the gamut of oculomotor pathology, and where the MLF is frequently affected, has never been described as causing spasm of convergence. Furthermore, none of the 44 autopsied cases of Wernicke's disease described by Victor, Adams and Collins (18) had involvement of the MLF. The lesions in cases of convergence spasm of organic nature are probably diffuse, implicating the oculomotor pathways passing in the thalamus (18), midbrain (17) and pons (19), but most likely spare the MLF.

Recently Jampel (20) induced convergence by electrode stimulation of Macaqua's occipital lobe. Nashold and Gills (21) in attempting to relieve intractable pain in man implanted electrodes in the midbrain and obtained among other ocular phenomena convergence spasms. Could then the convergence spasm result from an uninhibited or "overreacting" MLF? The answer to this question will have to be settled by experimentation.

Differential Diagnosis

The organic spasm of near reflex may have a central origin as well as a peripheral one. In lesions of central origin such as postencephalitis (2, 8, 9), Wernicke's syndrome (15), pineal tumors (1, 2, 14), and syndrome of the aqueduct of Sylvius (2) the patients are usually unaware of their symptoms because of depression of consciousness or mental confusion. Associated oculomotor disturbances such as defective horizontal conjugate gaze, limitation in vertical movements, pupillary abnormalities, and synkinetic movements are usually present (1, 2, 3, 5, 16).

Patients with convergence spasm of functional origin present with vision troubles as their chief complaint, but they also have a plethora of additional complaints, many of them unrelated to their vision difficulties. Their history will reveal usually a long list of emotional problems, sometimes psychiatric care in the past, often repeated hospitalization, and multiple "elective" operations (1, 2, 4, 5, 6).

Ocular spasm in these cases may be elicited by requesting the patient to move his eyes, as in our Case No. 2. Occasionally perfect orthophoria is noted in the very same position which elicited ocular spasm. Associated blepharospasm, and nystagmus of greater velocity than seen in neurologic disorders as well as long duration of the spasm may be present (1, 5, 7, 10). Finally and most importantly, the neurologic examination is normal.

Treatment

The ocular signs in Wernicke's disease disappear rapidly with thiamine administration (6, 15, 22) and this course was followed by our first patient. This case was complicated by the history of old head trauma and possibly by tabes, both having been associated with convergence spasm. The former was, however, of uncertain date and the latter was not thoroughly supported by the blood serology or the spinal fluid findings.

In bothersome cases of convergence spasm following head trauma associated with vertigo, phenobarbital has been tried (10) with moderate success.

Cycloplegiques and minus spheres are deemed helpful initially but later are discarded (1, 2) by most "functional" patients. Most authors agree (3, 4) that after a short trial, even eye muscle training should be discouraged lest the secondary gains of these patients, many of whom are hysterical, be perpetuated. Frank discussion of the problem when deemed advisable will apparently be sufficient in cases related more to anxiety than to conversion reaction (1, 5).

Summary

Two cases of convergence spasm are presented, the first of organic nature and the second of hysterical origin.

An alcoholic male was admitted with Wernicke-Korsakoff encephalopathy, sensory neuropathy, ataxia of the lower limbs, and gait difficulties. He denied vision troubles but oculomotor examination revealed two distinct types of disturbances: (a) bilateral limitation of abduction (b) convergence spasm. Under treatment with thiamine and penicillin for reactive VDRL, his mental status, affect and gait improved. His oculomotor abnormalities disappeared gradually.

The second case was that of a young woman with multiple ocular complaints having convergence spasm of hysterical origin. The spasm was present on straightforward gaze and easily elicited on target pursuit. Intravenous injection of sodium amobarbital eliminated the convergence spasm and resulted in orthophoria and excellent OKN. Unfortunately, the improvement did not persist.

These two cases underscore and appose the characteristic features of convergence spasm of organic and functional origin. In the first variety. the patient is unaware of the spasm and denies vision troubles. Various neurological findings are usually present but with treatment of the underlying disorder, the convergence spasm may disappear. In cases of functional origin, vision troubles are the usual presenting complaint. Associated multiple unrelated complaints are the rule. Ophthalmologic treatment including cycloplegiques, minus lenses, or eye muscle training are only temporarily helpful. Psychiatric counseling is of recognizable service. Sodium amobarbi-

tal proved useful in establishing the functional nature of the spasm in the second case.

Acknowledgments

The first patient's EOG and movie frame were recorded with Dr. Engleberg in Dr. Richard Burde's Neuro-ophthalmology Laboratory at the Barnes Hospital in St. Louis, Missouri. The second patient's EOG recording was done in the Neurophysiology Laboratory of Dr. B. Cohen at The Mount Sinai Hospital in New York City.

References

1. Cogan, D. C. and Freese, Jr., C. G.: Spasm of the Near Reflex, Arch Ophthalmol 54:752, 1955.
2. Walsh, F. B. and Hoyt, W.: *Clinical Neuro-Ophthalmology*. Baltimore, Williams and Wilkins Company, 1969, vol 3, p. 2529.
3. Bielschowsky, A.: Lecture on Motor Anomalies of the Eyes II – Paralysis of the Conjugate Movements of the Eyes, Arch Ophthalmol 13:569–583, 1935.
4. Duke-Elder, W. S.: *Neuro-Ophthalmology*, 1971, vol 12. p 832.
5. Willbrand, H. and Saenger, A.: Die Neurologie des Augen, Munchen, Bergman, JF 1921 vol 8.
6. Bender, M.B.: *Disturbances of Nervous Functions*. Edited by P. J. Vinken and G. W. Bruyn, in collaboration with R. Garcin Amsterdam, North-Holland Publishing Company, 1969, vol 1.
7. Curschman, H.: Uber Convergenzkrampfe bei Tabes Dorsalis, Neurol Centralbl 24, 10, 1905.
8. Delbeke K. and Van Bogaert, L.: Akinesie Postencephalitique A Forme Myasthenique, Encephale 23:855, 1928.
9. Houin, L.: Quoted by Delbeke and Van Bogaert.
10. De Morsier, G. and Balavoine, C.: Encephalopathie traumatique et spasm de la convergence, Rev Otoneuroophtalmol 21:400–403, 1949.
11. Kestenbaum A.: Clinical methods of Neuroophthalmology. Grune and Stratton, New York, Londong 1961, p. 453.
12. Yahr, M.: Personal communication.
13. Borries, G. V. T.: Konvergenzspasmus und Labyrinthleiden, Monatschr Ohrenh 10:736, 1926. Abstracted in Zentralbl ges Ophthal 17:912, 1927.
14. Kornblueth, W.: Transient Abolition of Pupillary Reaction to Convergence, Am J Ophthalmol 35:1815, 1952.
15. Thompson, R. A. and Lynde R. H.: Convergence Spasm Associated with Wernicke's Encephalopathy, Neurology (Minneap.) 19:711–712, 1969.
16. Verbiest, H. M.: Observation sur le mechanisme de la convergence myotonique dans un cas de maladie de Steiner, Rev Neurol 67:387, 1937.
17. Bender, M. B. and Weinstein, E. A.: Effects of Stimulation and Lesions of the M.L.F. in the Monkey, Arch Neurol Psych 52:106–113, 1944.
18. Victor, M., Adams, R.D., and Collins, H. G.: *The Wernicke-Korsakoff Syndrome*. Contemporary Neurology Series, Ed., Davis Company 1971.
19. Cohen, B., Komatzukai, A., and Bender, M. B.: Electro-oculographic Syndrome in Monkeys after Pontine Reticular Formation Lesions, Arch Neurol (Chicago) 18:78, 1968.
20. Jampel, R. S.: Vergence Eye Movements, J Compl Neurol 115:371, 1960.
21. Nashold, B. S. and Gills, J. P.: Ocular Signs Resulting from Brain Stimulation and Lesions in the Human, Arch Ophthalmol 77:609–618, 1967.
22. Merritt, H.: *Textbook of Neurology*. Lea & Febiger, Philadelphia, 1976.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

Hypogammaglobulinemia Associated with Kaposi's Sarcoma

SHENG-CHI WANG, M.D. AND STEPHEN A. GELLER, M.D.

Abstract

Hyperimmunoglobulinemia has been associated with Kaposi's sarcoma. Many patients have normal immunoglobulins. This report describes a patient with widespread Kaposi's sarcoma in whom clinically documented extreme hypoimmunoglobulinemia was a diagnostic problem.

Kaposi's sarcoma is generally regarded as a relatively low grade cutaneous malignancy which may, on occasion, metastasize widely (1–4). Hypergammaglobulinemia has been described in association with Kaposi's sarcoma (5–7), but hypogammaglobulinemia appears to be distinctly unusual. We recently had the opportunity of studying a patient with widespread Kaposi's sarcomatosis in whom hypogammaglobulinemia was a diagnostic problem.

Case Report

A 73-year-old white women was readmitted to The Mount Sinai Hospital in July, 1971, because of worsening pruritis, increasing fatigability, weight loss and abdominal distention. She had been well until December, 1961, when she underwent ligation and stripping of venous varicosities of the left leg. In June, 1969, a lesion excised from her left lower leg was diagnosed as Kaposi's sarcoma. In October, 1970, the diagnosis of diabetes mellitus was made, and she was treated with an oral hypoglycemic agent (phenformin hydrochloride). The total serum protein determination at that time was 5.3 gm/200 ml with a globulin of 1.8 gm./100 ml. In May 1971, she was admitted to another hospital for night sweats and hepatosplenomegaly. A liver biopsy showed nondiagnostic granulomata, and she was transferred to The Mount Sinai Hospital.

She complained of pruritis, easy fatigability, night sweats, weight loss, and abdominal distention. Liver biopsy was repeated and again demonstrated granulomata, the etiology of which was not determined. In spite of a negative tuberculin skin test, she was placed on antituberculous therapy and discharged. Her symptoms worsened, however, precipitating the final hospitalization.

At admission, she was in mild respiratory distress, anemic, and mildly icteric. Her temperature was 99°, blood pressure 118/50 mm Hg, pulse 98/min and irregular, respirations 30/min. Microaneurysms were seen in both optic fundi. Ascites, hepatomegaly and splenomegaly were demonstrable. Cervical, right axillary and inguinal lymph nodes were enlarged. An ulcerated, irregular, partially necrotic vascular lesion was on the left lower leg.

The hemoglobin level was 9.0 gm/100 ml, hematocrit was 27 percent and the white blood cell count was 10,800 cells/ml. The serum bilirubin value was 3.5 mg/ml and the alkaline phosphatase activity was 850 U (normal 30-85). The fasting blood sugar level was 165 mg/100 ml. The total serum protein was 5.0 gm/100 ml with an albumin of 2.88 gm/100 ml. The alpha 1 globulin was 0.52 gm/100 ml, the alpha 2 globulin was 0.56 gm/100 ml, the beta globulin 0.82 gm/100 ml,

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From the Department of Pathology, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029; and the Department of Pathology, Sharon General Hospital, Sharon, Pa. 16146.

Requests for reprints should be sent to: Stephen A. Geller, M.D., Department of Pathology, Mount Sinai School of Medicine, Fifth Avenue and 100 Street, New York, N. Y. 10029.

and the gamma globulin 0.13 gm/100 ml. Quantitative immunoelectrophoresis showed an IgG of 72 mg% (normal 900–1500), and IgA of 16 mg% (normal 210–390) and an IgM of 16% (normal 80–120). Direct and indirect Coomb's tests were negative and the haptoglobulin was 110 mg%. Attempts to culture acid-fast bacilli from urine, sputum, ascitic fluid, bone marrow aspirate, and liver biopsy specimen were negative. A right pleural effusion and right lower lobe infiltrate were seen on chest roentgenography.

The hypogammaglobulinemia, hepatosplenomegaly, lymphadenopathy and rapid worsening of the patient's condition suggested the diagnosis of a coexisting malignant lymphoma or Hodgkin's disease, and she was treated with Cytoxan, Vincristine, corticosteroids, and testosterone. She became leukopenic, increasingly icteric and azotemic and died on the 52nd hospital day.

Necropsy

Widespread Kaposi's sarcoma, involving cutaneous surfaces and visceral organs, was found at autopsy. The visceral lesions were dark red, circumscribed, vascular nodules varying from 0.5 cm to 3 cm in diameter. These nodules involved the heart, lungs, liver, spleen, pancreas, adrenals, lymph nodes, stomach, small intestine, and gall bladder.

The liver weighed 2100 gm and the parenchyma was partially replaced by discrete and coalesced tumor nodules. The enlarged spleen weighed 540 gm; and large irregular vascular spaces obscured the architecture (Fig. 1). The mediastinal, pulmonary hilar, periaortic, peripancreatic, mesenteric, cervical, axillary and inguinal lymph nodes were all enlarged and replaced by tumor (Fig. 2). The thymus was not identified. The skin was marked by multiple slightly elevated, violaceous tumor nodules, most of them less than 0.6 cm in diameter. The nodules were present in the skin of the chest, in the inguinal region and over both lower extremities. Histologically, the well-

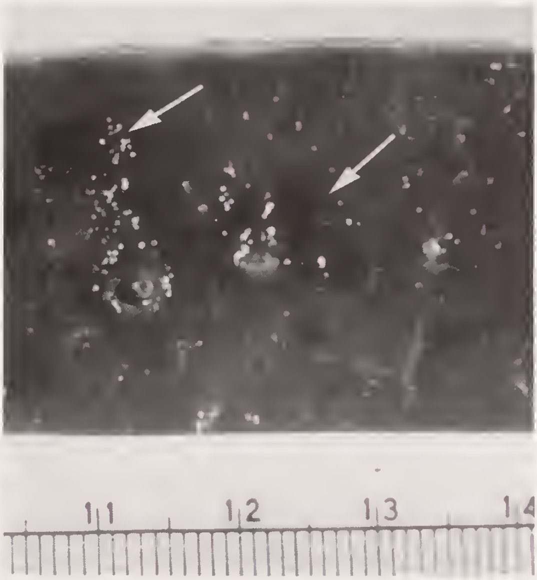


FIG. 1. Spleen showing poorly circumscribed violaceous tumor nodules (arrow).

FIG. 2. Photomicrograph of lymph node completely replaced by tumor tissue. (hematoxylin-eosin, original magnification × 10).

circumscribed tumor nodules consisted of many irregular vascular channels, lined by slightly prominent endothelial cells, separated by highly atypical hyperchromatic spindle cells (Fig. 3). Within the sheets of spindle cells, were extravasated red blood cells, hemosiderin and scattered collections of small lymphocytes.

Discussion

Kaposi's sarcoma is a relatively uncommon neoplasm in the United States with a particular prevalence in Jews (8). By contrast, it is common in Central Africa, with a geographic distribution similar to that of Burkitt's lymphoma (9). Master studied 60 patients with Kaposi's sarcoma in Uganda (10). Immunoglobulins were studied in all of these patients and were within normal ranges.

Kaposi's sarcoma has been associated with disorders of the reticuloendothelial system (11, 12). The association of this tumor with malignant lymphoma (13, 14), Hodgkin's disease (15, 16), multiple myeloma (17, 18), thymoma (2, 19) and leukemia (20) is well known. In many of these cases hypogammaglobulinemia has been documented with the secondary lymphoreticular malignancy.

Kaposi's sarcoma has developed in patients with hypoimmunoglobulinemia after treatment with immunosuppressive agents following renal transplantation (21, 22) and it has been suggested that the development of the tumor followed iatrogenic impairment of immunologic surveillance. In these cases, of course, hypogammaglobulinemia preceeded the development of the tumor.

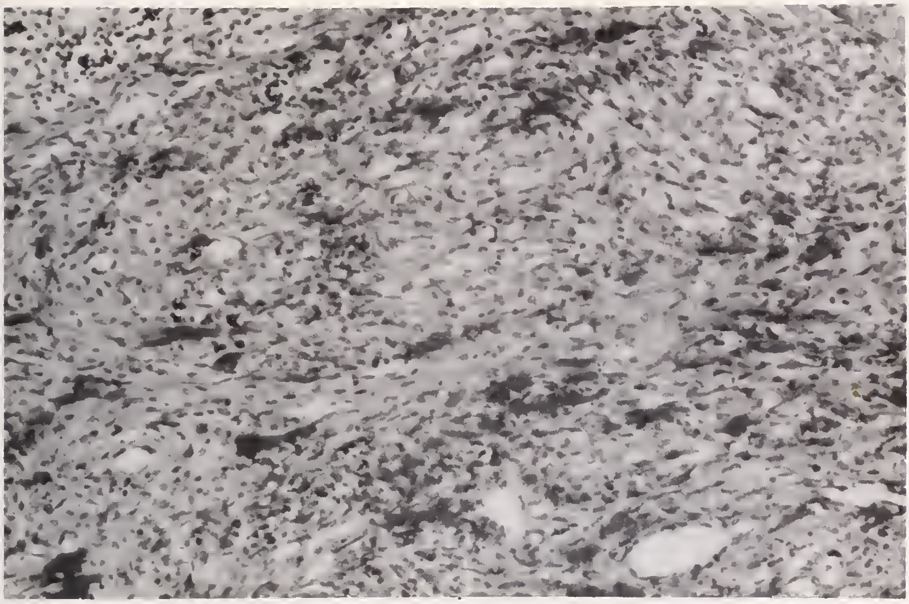


FIG. 3. Photomicrograph of tumor showing prominent vascular channels separated by sheets of hyperchromatic spindle cells, with extravasated red blood cells, small lymphocytes and hemosiderin pigment (hematoxylin-eosin, original magnification × 40).

Hepatosplenomegaly, lymphadenopathy and extreme hypogammaglobulinemia in a patient known to have Kaposi's sarcoma, suggested the diagnosis of associated malignant lymphoma or Hodgkin's disease in the present case. Rather than having a lymphoma, the lymphoid tissues in this case were extensively replaced by Kaposi's sarcoma. Hypogammaglobulinemia may have been the result of replacement of lymphorecticular tissues by the widely disseminated tumor. The clinical documentation of low immunoglobulins in a patient with Kaposi's sarcoma, may indicate wide dissemination of the primary tumor and need not be considered diagnostic of a malignant lymphoma.

References

1. Stats, D.: Visceral Manifestation of Kaposi's Sarcoma, J Mount Sinai Hosp 12:971, 1946.
2. Maberry, J. D., and Stone, O. J.: Kaposi's Sarcoma with Thymoma, Arch Dermat 95:210, 1967.
3. Case records of The Massachusetts General Hospital, Case 30-1971, N Engl J Med 285:279, 1971.
4. Templeton, A. C.: Studies in Kaposi's Sarcoma. Postmortem Findings and Disease Patterns in Women, Cancer 30:854, 1972.
5. Ecklund, R. E. and Valaitis, J.: Kaposi's Sarcoma of Lymph Nodes, Arch Path 74:224, 1962.
6. Rywlin, A. M., Recher, L., and Hoffman, E.: Lymphoma-like Presentation of Kaposi's Sarcoma. Three Cases without Characteristic Skin Lesions, Arch Dermat 93:554, 1966.
7. Lubin, J., and Rywlin, A. M.: Lymphoma-like Lymph Node Changes in Kaposi's Sarcoma. Two Additional Cases, Arch Path 92:338, 1971.
8. Bleufarb, S. M.: *Kaposi's Sarcoma*. Charles C Thomas. Springfield, Ill. 1955.
9. Cook, P. J. and Burkitt, D. P.: Cancer in Africa, Brit Med Bull 27:14, 1971.

10. Master, S. P., Taylor, J. F., Kyalwazi, S. K., and Ziegler, J. L.: Immunological Studies in Kaposi's Sarcoma in Uganda, Brit Med J 1:600, 1970.
11. Tedeschi, C. G.: Some Consideration Concerning the Nature of so-called Sarcoma of Kaposi, Arch Path 66:656, 1958.
12. Uys, C. T., and Bennet, M. B.: Kaposi's Sarcoma: A neoplasm of Reticular Origin, S Afr J Lab Clin Med 5:39, 1959.
13. Bleufarb, S. M. and Webster, J. R.: Kapsoi's Sarcoma Associated with Lymphosarcoma, Arch Int. Med 91:97, 1953.
14. Epstein, E.: Extracutaneous Manifestation of Kaposi's Sarcoma. A Systemic Lymphoblastoma, Calif Med 87:98, 1957.
15. Greenstein, R. H., Conston, A. S.: Co-existent Hodgkin's Disease and Kaposi's Sarcoma, Am J M Sc 218:384, 1949.
16. Brunning, R. D., Foley, J. F., and Fortuny, I. E.: Hodgkin's Disease and Kaposi's Sarcoma. Report of a Case, Arch Int Med 112:363, 1963.
17. Reynolds, Q. A., Winklemann, R. K., and Soule, E. H.: Kaposi's Sarcoma: A clinicopathologic Study with Particular Reference to Its Relationship to the reticulo-Endothelial System, Medicine 44:419, 1965.
18. Mazzaferri, E. L. and Penn, G. M.: Kaposi's Sarcoma associated with Multiple Myeloma. Report of a Patient and Reveiw of the Literature, Arch Int Med 122:521, 1968.
19. Gellin, G. A.: Kaposi's Sarcoma. Three Cases, of Which Two Have Unusual Findings in Association, Arch Dermat 94:92, 1966.
20. Fischer, J. W. and Cohen, D. M.: Simultaneous Occurrence of Kaposi's Sarcoma, Leukemia and Diabetes Mellitus. Report of a Case, Am J Clin Path 21:586, 1951.
21. Siegel, J. H., Janis, R., Alper, J. C., Schutte, H., Robbins, L., and Blaufox, M.D.: Disseminated Visceral Kaposi's Sarcoma. Appearance after Human Renal Homograft Operation, JAMA 207:1493, 1969.
22. Myers, B. D., Kessler, E., Levi, J., Pick, A., Rosenfeld, J. B.: Kaposi Sarcoma in Kidney Transplant Recipients, Arch Int Med 133:307, 1974.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July-August 1977
Printed in U.S.A.

Influence of Brain Metastases on the Chemotherapeutic Management of Breast Cancer: A Case Report

ALEXANDER W. PEARLMAN, M.D.

It has been estimated that the overall cure rate for breast cancer does not exceed 30%. The majority of patients will, sooner or later present themselves with metastatic disease requiring systemic therapy either by hormonal manipulation or nonhormonal chemotherapy (3). This paper is concerned with intracranial metastases and the role of the brain as a sanctuary in patients undergoing chemotherapeutic treatment.

The actual incidence of central nervous system metastases in advanced breast cancer is difficult to establish. For many patients, the disease remains clinically silent for long periods and is often overshadowed by disease in other more obvious metastatic sites. Death may occur before the presence of intracranial metastases is suspected. The incidence based on autopsy material can be misleading since examination of the brain is ofttimes omitted. The incidence of intracranial metastases is unquestionably understated.

Bunting et al (1) recorded the incidence of recurrence by site in 348 patients with breast cancer followed for five to 22 years. Five percent of recurrence appeared in the brain. Over 80% of patients with local recurrences ultimately develop distant metastases. Patients with mastectomy scar recurrence have an even higher incidence of distant blood-borne metastases (2). Of all patients with intracranial metastases a primary breast cancer has been implicated in various series in from five to 34% of patients (3, 4).

Brambilla et al (5) reported a complete or partial response to chemotherapy in 38 to 60 percent of their patients depending on the dominant site of metastases but in 5 of 105 patients, approximately 5%, new diseases appeared in the central nervous system during treatment. A similar experience is reported by Cannellos et al (6), who treated 40 patients, none of whom had evidence of CNS disease. All 35 responders ultimately relapsed and five (15%) developed CNS disease. In Greenspan's series (11) there were 40 patients with advanced breast cancer treated with thiotepa and methotrexate. Eight had CNS metastases (in addition to other sites), an incidence of 20%. Five of the eight patients responded to treatment but all received whole brain irradiation simultaneously with chemotherapy. It would appear from the foregoing that intracranial metastases has an expected incidence of between 5 and 20%.

The role of chemotherapy in advanced breast cancer is well defined. Several

From the Department of Radiation Therapy, Hospital for Joint Diseases and Medical Center, 1919 Madison Avenue, New York, N. Y. 10035

Requests for reprints should be sent to: A. W. Pearlman, M.D., Hospital for Joint Diseases, 1919 Madison Avenue, New York, N. Y. 10035.

clinically useful chemotherapeutic agents may be used either singly or more effectively, in combinations of several active drugs.

Combined chemotherapy is associated with improved regression rates and more prolonged remissions (5–10). Greenspan (8) has estimated that multiple simultaneous drug therapy can induce a clinically recognizable remission in 60 to 80% of unselected metastatic patients, whether or not previous hormone ablation was successful. The drugs most commonly employed are 5 fluorouracil, methotrexate, alkylating agents (cytoxan, thiotepa or melphalan) adriamycin and vincristine, with or without steroids. However, with the occasional exception of high dose, pulsed, IV methotrexate (11), none of these agents attain sufficient prolonged concentration in the central nervous system to be effective against intracranial metastatic disease.

Given a significant incidence of intracranial metastases and a group of chemotherapeutic drugs with a high degree of therapeutic efficiency except for the CNS, there will be a number of patients in whom the brain will act as a sanctuary. This is illustrated by the following case report.

Case Report

S. B., A white female, aged 33 years, first noticed a mass in the upper outer quadrant of her right breast measuring approximately 2.5 cm in diameter one month prior to surgery. There were no palpable axillary nodes. Her past history included the use of birth control pills for five years following her only pregnancy which ended in spontaneous abortion. For the year prior to her present illness, she had discontinued the birth control pills but was unable to conceive. Her menstrual cycle was regular. Her mother died of metastatic breast cancer at age 47. Two sisters aged 37 and 31 years were well.

She underwent right radical mastectomy and left breast biopsy. Histologically the breast mass was a lobular carcinoma and only one of 17 lymph glands was positive. The clinical classification was T2NoMo and the surgical T2N1Mo, Stage II. Surgery was followed by Cobalt 60 irradiation. This was limited to the internal mammary chain, supraclavicular nodes and apex of the axilla. The tumor dose was 4400 rads in 29 days.

After a "free interval" of 9 months, the first recurrence appeared in the mastectomy scar, followed in rapid succession by multiple large subcutaneous deposits, more or less limited to the scar area. No other metastatic lesions could be demonstrated. Since she was still menstruating, she underwent bilateral oopherectomy. Abdominal exploration revealed no evidence of metastatic disease. Following castration, the chest wall lesions continued to increase rapidly in size.

It was felt that further hormone manipulation would offer little hope of success. Clinical investigation revealed skeletal survey, bone and liver scan, chemistries and blood count all normal except for elevation of the LDH. Chest radiographs did, however, reveal the presence of a right pleural effusion and 600 ml of serosanginous fluid was aspirated.

The entire right anterior chest wall was irradiated with large medial and lateral, opposing, tangential fields to a midline tumor dose of 3500 rads in 21 days with Co60. The masses shrank almost completely by the conclusion of treatment. In view of the gravity of a mastectomy scar recurrence, irradiation was followed immediately by systemic chemotherapy. Each course consisted of weekly intravenous injections of 5 fluorouracil (600 mg per m^2) and methotrexate (40 mg per m^2) X2 and oral cytoxan (150 mg P.O.) daily for 14 days. After a 2 week rest period, the course was repeated. She received 6 courses over a 6-month period. While undergoing chemotherapy, all objective evidence of disease disappeared. She returned to full employment with a performance status of 10 (Diamond). There was one mild, self-limited episode of herpes zoster.

Shortly after the last course of chemotherapy, she suddenly experienced dizziness, difficulty ambulating, severe headaches, and vomiting. Three was papilledema and a brain scan (Fig. 1) showed multiple metastatic lesions, the largest in the cerebellum. She rapidly became obtunded despite high doses of steroids and an attempt at whole brain irradiation. Death occurred in deep coma, one year, five months after mastectomy and 9 months after her first scar recurrence.

Autopsy: Complete autopsy was performed. Multiple metastatic lesions were present throughout the brain. The largest in the cerebellum (Fig. 2) which measured 3 cm in diameter showed evidence of central necrosis and liquefaction. There were only two small foci of metastatic cancer outside the brain. A 1 cm nodule in the apex of the left lung and a 3 cm nodule in the right lung base adjacent to the pericardium. All other organs were free of cancer.

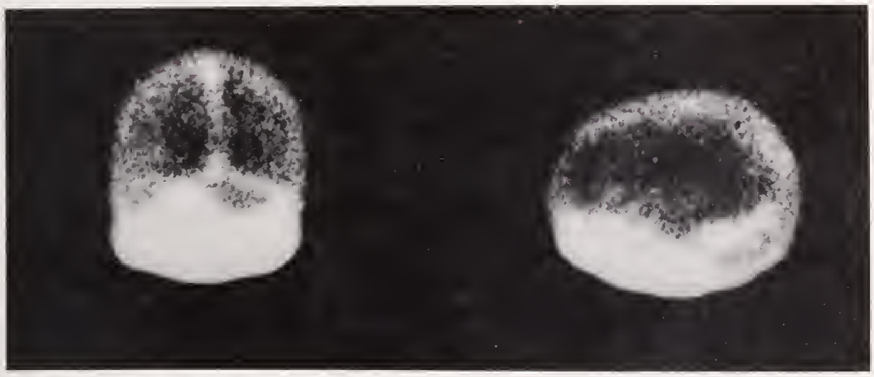


FIG. 1. Brain scan (99m Technetium pertechnetate). Posterior and lateral projections demonstrate a large metastatic focus in the left cerebellum. Smaller metastatic foci are present in the frontal, parietal and temporal lobes (autopsy proven).

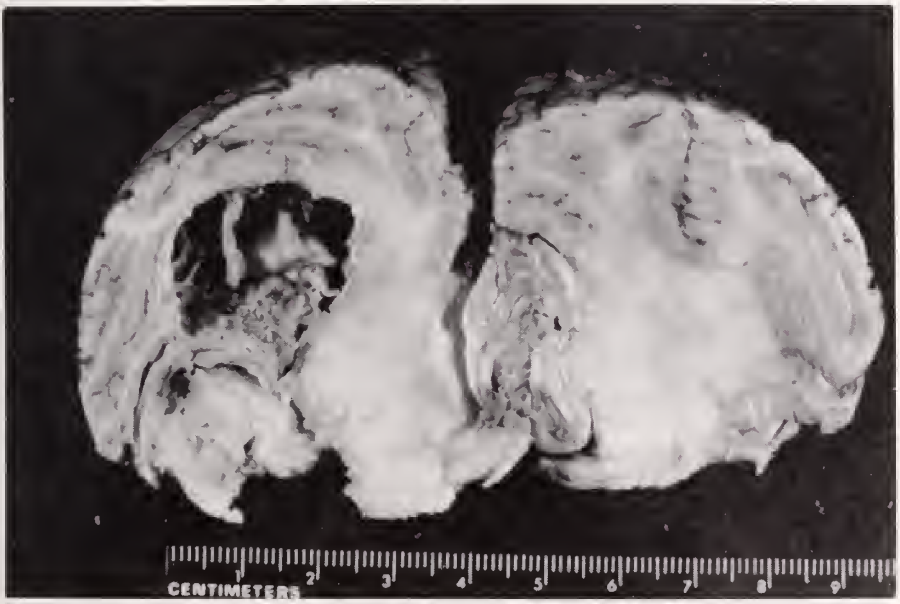


FIG. 2. A 3 cm metastatic lesion occupies the left cerebellar hemosphere. There is central necrosis and liquefaction. This is the large lesion demonstrated on brain scan. Multiple small discrete metastatic foci were present throughout the brain.

Biomathematics of Tumor Growth

The following biomathematical considerations are based on the sequence of events in this patient and help to clarify the clinical course. The tumor doubling time (Td), the time during which there is a twofold increase in tumor volume, can be calculated when the first manifestations of metastatic disease appears in the mastectomy scar at a known interval after mastectomy. This assigns a mathematical number to the malignant potential of a tumor and serves as a useful clinical parameter (12, 13). Assuming the constant growth rate for malignant tumors from the time of their inception till they reach at least a moderate size, approximately 2 to 2.5 cm in diameter (14, 15), it requires 30 tumor volume doublings for a single cell to attain a diameter of 1 cm, which is generally considered the smallest clinically diagnosable size. This period of microscopic growth may comprise as much as 75% of the entire life cycle of the tumor. Unrestrained growth thereafter would lead to a huge tumor, incompatible with life after relatively few additional doublings (2). During this long clinically silent period, occult metastatic spread may occur, with all that this implies in the management and prognosis of the patient.

This patient's calculated Td was 8 days, based on the interval from mastectomy to scar recurrence. This would place the tumor in the category of rapid growth, Td up to 25 days (12). There are two additional biomathematical considerations of clinical significance that warrant further comment. The first of these related to the probable time of onset of the cerebral metastases relative to the overall clinical course. For the cerebellar tumor to have reached a diameter of 3 cm after implantation would have required at least 32 tumor volume doublings. By backward extrapolation, assuming the same Td as the original scar recurrence and a constant growth rate, the minimal time that the largest cerebral metastasis could be present would approximate 250 days. It would likely have been present even longer since the anoxia and central necrosis were undoubtedly associated with slowing of the growth rate. This places the onset of the brain metastasis at least as early as and possibly prior to the appearance of the scar recurrence. The implication of this is that the brain metastases continued to grow during the chemotherapeutic treatment.

The second consideration relates to the patients overall survival and whether or not it was prolonged by treatment. She survived 1 6/12 years after mastectomy. Survival measured in units of time is related to the rapidity of tumor growth and therefore is not necessarily a parameter of the effectiveness of the treatment. Patients with slow growing tumors tend to survive for long periods even in the face of metastatic disease. When survival is cacualted in multiples of tumor doublings, differences in longevity related to tumor growth rates, disappear (2). This patient survived 67 tumor doublings after mastectomy. In a previous paper the author presented the cumulative mortality of a series of patients with scar recurrence followed to death measured in mulitples of tumor volume doublings. This patient falls into the 70th percentile. Only 30% of the cohort survived this many tumor doublings

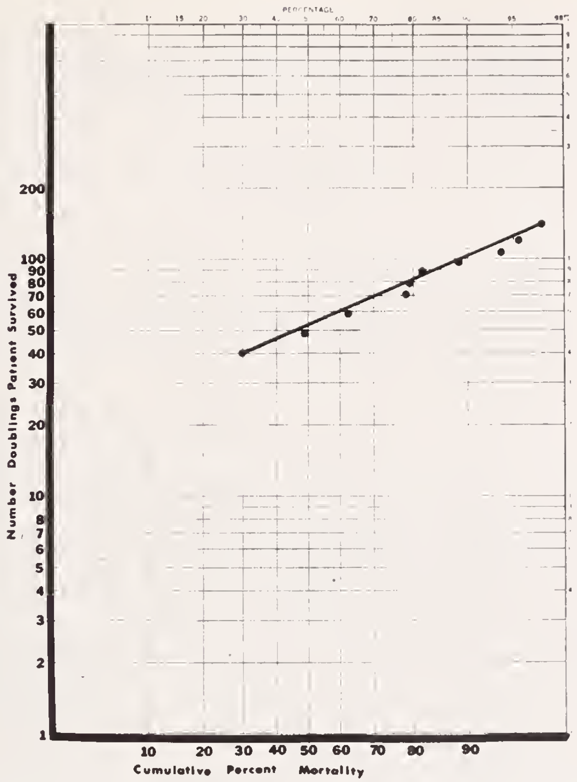


FIG. 3. Cumulative percent mortality in a series of 80 patients whose first metastasis appeared in the mastectomy scar. Longevity is measured in multiples of tumor doublings. This patient who survived 67 tumor doublings falls into the 70th percentile.

(2). This is probably a more accurate indication of therapeutic efficiency than survival in units of time and suggests that for this patient, survival was prolonged by chemotherapy beyond the expected average, despite the continued growth of central nervous system metastases (Fig. 3).

The presence of CNS metastases may be expected in a clinically significant percent of patients with advanced metastatic breast cancer. The routine treatment of such patients with combinations of chemotherapeutic drugs that do not concentrate adequately in the brain, dooms these patients to failure unless early diagnosiss is combined with adjuvant therapy such as whole brain irradiation.

References

1. Bunting, J. S., Hemsted, E. H., and Kremer, J. K.: The Pattern of Spread and Survival in 596 Cases of Breast Cancer Related to Clinical Staging and Histological Grade, Clin Radiol 27:9–15, 1976.
2. Pearlman, A. W.: Breast Cancer: Influence of Tumor Growth Rate on Survival. Cancer (To be published).
3. Abrams, H. L., Spiro, R., and Goldstein, N.: Metastases in Carcinoma, Cancer 3, 74:1950.
4. Fuller, L. M., Milam, E., Leavans, M. D., Eckles, N. E., and Sears, M. E.: Management of

Metastases from Carcinoma of the Breast to Central Nervous System and the Eye. Breast Cancer Early and Late. Year Book Medical Publishers, 1968, Chicago.

5. Brambilla, C., DeLena, M., Rossi, A., Valagussa, P., and Bonadonna, G.: Response and Survival in Advanced Breast Cancer after Two Non-Cross Resistant Combinations, Brit Med J 1:801-804, 1976.
6. Canellos, G. P., Gold, G. L., Schein, P. S., and Young, R. C.: Combination Chemotherapy for Advanced Breast Cancer: Response and Effect on Survival, Ann Int Med 84:389-392, 1976.
7. Brunner, K. W., Sonntag, R. W., Martz, G., Senn, H. J., Obrecht, P., and Alberto, P.: A Controlled Study in the Use of Combined Drug Therapy for Metastatic Breast Cancer, Cancer 36:1208-1219, 1975.
8. Greenspan, E. M.: Breast Cancer Protocols, Mount Sinai School of Medicine, 1972.
9. Greenspan, E. M., Fieber, M., Lesnick, G., and Edelman, S.: Response of Advanced Breast Cancer to Combination of Antimetabolite, Methotrexate, and the Alkylating Agent, Thiotepa, J Mount Sinai Hosp 30:246-267, 1963.
10. Jones, S. E., Durie, B. G. M., and Salmon, S. E.: Combination Chemotherapy with Adriamycin and Cyclophosphamid for Advanced Breast Cancer, Cancer 36:90-97, 1975.
11. Tattersall, M. H. N., Parker, L. M., Pitman, S. W., and Frei, III, E.: Clinical Pharmacology of High Dose Methotrexate (NSC-740), Cancer Chemother Rep 6:25-29, 1975.
12. Collins, V. P., Loeffler, R. K., and Tivey, H.: Observations on Growth Rates on Human Tumors, Am J Roentogenol 76:988, 1956.
13. Schwartz, M.: A Biomathematical Approach to Clinical Tumor Growth, Cancer, 14:1272, 1961.
14. Garland, L. H.: The Rate of Growth and Natural Duration of Primary Bronchial Cancer, Am J Roentgenol 96:604, 1966.
15. Garland, L. H.: Coulson, W., and Wollin, E.: The Rate of Growth and Apparent Duration of Untreated Primary Bronchial Cancer, Cancer 16:694, 1963.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

Serial Echocardiography of the Aortic Valve in Bacterial Endocarditis: A Case Report*

ROBERT F. REDER, M.D. HSU-CHONG YEH, M.D. IVAN DIMICH, M.D. AND LEONARD STEINFIELD, M.D.

Abstract

A case report of a young boy with rheumatic valvular disease and bacterial endocarditis is presented. Serial electrocardiograms display the transition from normal to an abnormal aortic valve region as the disease progresses. The pathologic and echocardiographic findings correlate closely.

Bacterial endocarditis can be difficult to diagnose in the face of sterile blood cultures. Recent reports (1–14) have indicated that echocardiography is a useful adjunct in the diagnosis of bacterial endocarditis by virtue of its ability to detect the valvular vegetations and leaflet alterations associated with this disease. With use of serial echocardiographic studies, the evolution of certain facets of aortic valve pathology coincident with bacterial endocarditis are easily assessed. Echocardiograms may provide specific information which can help in either the establishment of a diagnosis or in the determination of appropriate medical and/or surgical therapy.

The following case report of a boy with bacterial endocarditis complicating rheumatic heart disease is the first to present serial echocardiograms which display the transition from a normal to an abnormal aortic valve region as a result of bacterial endocarditis. Relevant anatomic data is presented.

Case Report

The patient, a 10-year-old boy, was first admitted to the hospital in May 1975 with a sore throat, abdominal pain, low-grade fever, polyarthritis, and a blowing, apical systolic heart murmur compatible with mitral regurgitation. The initial laboratory work—including an ESR of 135 mm/hr; WBC, 15,100/mm^3; CRP, +3; ASLO, 1200 T.U.; a normal ECG; a normal chest roentgenogram; and sterile blood cultures—supported the diagnosis of acute rheumatic fever. During that hospitalization the heart murmur did not change, but transient prolongation of the PR interval to 0.2 seconds (heart rate, 110/min) developed. Treatment consisted of bed rest, aspirin, and intramuscular benzathine penicillin. His symptoms abated. Echocardiography (Fig. 1) revealed a normal aortic valve and root. No vegetations were noted on the mitral valve. At the time of discharge, the patient continued to have an elevation of the ESR and a soft blowing apical systolic murmur suggestive of mild mitral regurgitation.

The patient returned to clinic on June 9. Examination revealed mild mitral insufficiency. An ESR was 100 mm/hr. Benzathine penicillin prophylaxis was administered. On June 18 a second echocardiogram was unchanged from the first study in the hospital. On June 30 he again received intramuscular benzathine penicillin.

From the Departments of Pediatrics and Radiology, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Requests for reprints should be sent to: Robert F. Reder, M.D., Division of Pediatric Cardiology, Department of Pediatrics, Mount Sinai School of Medicine of The City University of New York, Fifth Avenue and 100 Street, New York, N.Y. 10029.

* Supported in part by a NIH training grant A 100445.

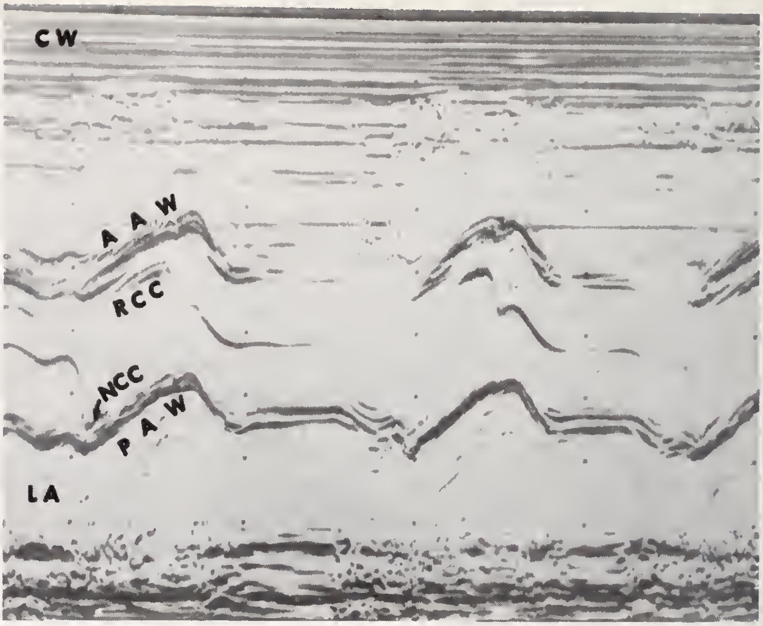


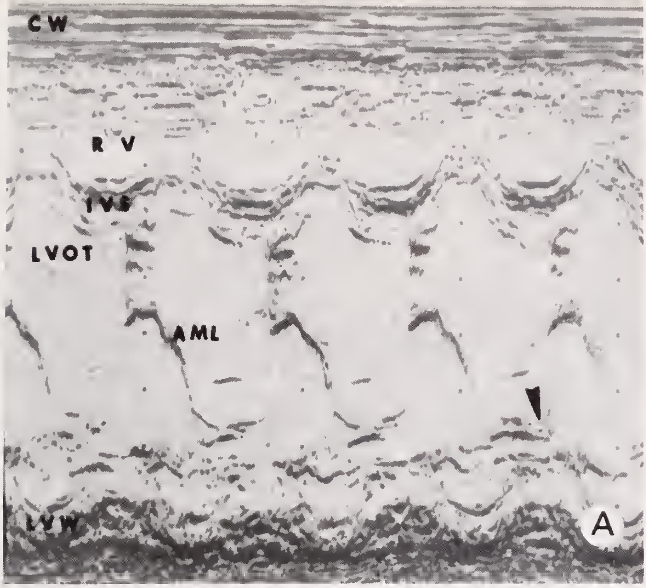
FIG. 1. Echocardiographic examination of the aortic root prior to the episode of bacterial endocarditis. The examination is considered normal. AAW – Anterior aortic wall; CW – chest wall; LA – left atrium; NCC – non-coronary cusp; PAW – posterior aortic wall; RCC – right coronary cusp.

The patient was readmitted on July 21 with a 4-day history of high fever, vomiting and abdominal pain. Initial examination revealed a rectal temperature of 103° F; blood pressure, 110/80; normal peripheral pulses; a blowing apical systolic murmur; and normal heart size. The liver and spleen were not palpable. The CRP was +4; ASLO > 2400 T.U.; ESR, 100 mm/hr; and WBC, 16,200/mm^3. Multiple sets of blood cultures were sterile. Diagnostic considerations during the first week of hospitalization included bacterial endocarditis, recurrent rheumatic fever, and generalized collagen-vascular disease. Because no specific diagnosis could be made, treatment consisted of aspirin, corticosteroids, and 42 days of parenteral antibiotics. Multiple cultures of the blood, bone marrow, and cerebrospinal fluid revealed no growth.

The patient's hospital course was one of slow, progressive deterioration. The course was complicated by the insidious development of aortic insufficiency and congestive heart failure. Over a period of four weeks, a II/VI diastolic decrescendo murmur at the left sternal border, bounding peripheral pulses, cardiomegaly, hepatomegaly, and a widened pulse pressure developed. A third echocardiogram performed on the 29th day of hospitalization (Figs. 2A and B) was interpreted as showing a marked thickening of the posterior (noncoronary) and a noticeable thickening of the anterior (right coronary) aortic cusps probably due to vegetations, prolapse into the left ventricular outflow tract of a torn aortic cusp or vegetation, or both, and fluttering of the mitral valve due to aortic regurgitation. In addition, an enlarged left atrium, a large ventricle, and marked septal motion were noted. There was no evidence of vegetations on the mitral valve.

The patient was maintained in a marginal state of compensation on a treatment regimen consisting of cardiotonic agents, antibiotics, and corticosteriods until the 71st day of that hospitalization when he suddenly expired. Aortic valve replacement was being considered at the time of demise.

A postmortem examination of the heart showed small rheumatic lesions on the mitral and aortic valves. Small vegetations of healed bacterial endocarditis were noted on the mitral valve. On the aortic valve (Fig. 3) the right coronary cusp was noted to be torn and to have



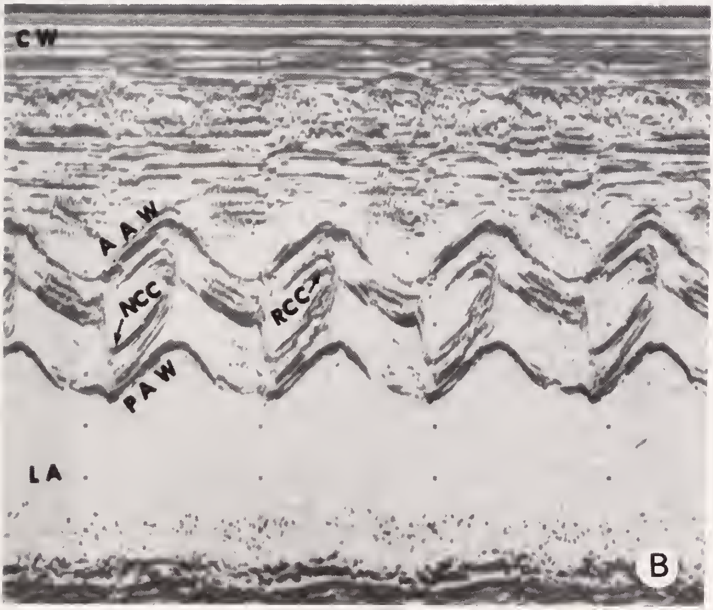


Fig. 2A. Final echocardiogram obtained on this patient. Most noteworthy are the diastolic echoes seen in the left ventricular outflow tract. These represent prolapsing of an aortic valve cusp or vegetation, or both, into this region during diastole. AML – anterior mitral leaflet; CW – chest wall; IVS – interventricular septum; LVOT – left ventricular outflow tract; LVW – left ventricular wall; RV – right ventricle. Arrow indicates mitral valve echo.

Fig. 2B. Aortic root study of final echocardiogram. Note the thickened aortic cusp echoes in systole and diastole. The thickening of the cusp echoes was interpreted as being a reflection of vegetations on the cusps. In systole, some thickening of the right coronary cusp echoes corresponds to the thickening of the torn right coronary cusp on the pathological specimen (Figure 3). Marked thickening of noncoronary cusp also corresponds well with the large vegetation seen on this cusp on the pathologic specimen. The left coronary cusp echoes were not seen on this study. The excursion of these cusps seems normal. Abbreviations are the same as Figure 1.

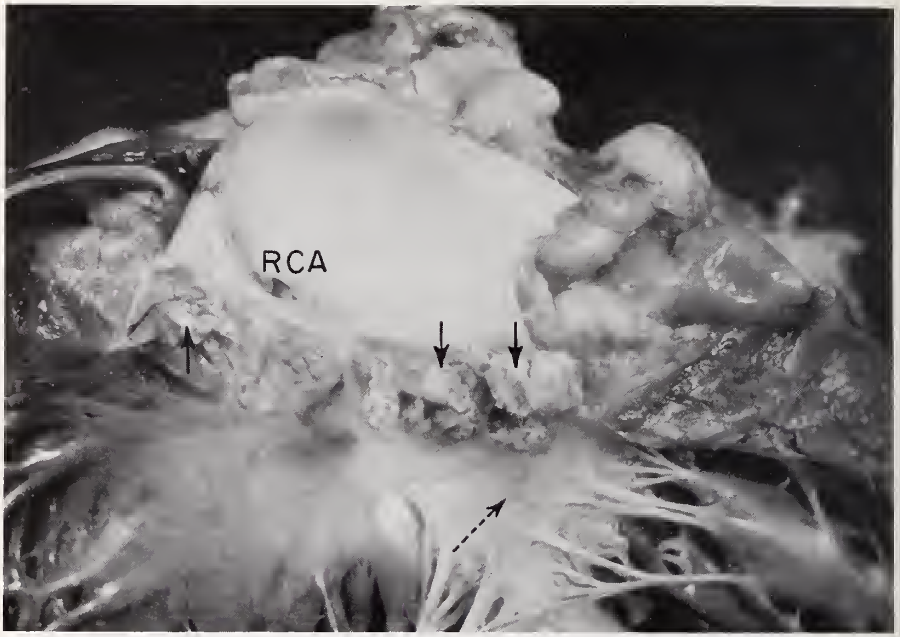


FIG. 3. Aortic valve. Torn, deformed right coronary cusp is seen below the orifice of the right coronary artery (RCA). Large vegetations (solid arrows) are indicated on the left and noncoronary cusps. On the aortic side of the anterior leaflet of the mitral valve (dotted arrow), a small vegetation and ulcer are noted below the junction of the noncoronary and left coronary cusps.

vegetations upon it. The noncoronary and especially the left coronary cusps were replaced by large vegetations of healed bacterial endocarditis. There was an ulcer on the aortic side of the anterior mitral leaflet. In the abdomen a large splenic infarction was noted.

Discussion

In cases of actual or suspected bacterial endocarditis, properly performed echocardiograms can yield information regarding aortic valve morphology that may otherwise be unobtainable (1–14). Recent evidence suggests that adults with bacterial endocarditis who require surgical intervention are those with echocardiographic evidence of valvular vegetations (14). While some authors (11, 15) have taken the view that the echocardiographic features of aortic valve vegetations are not necessarily specific, most (3, 5, 8, 10, 12) suggest that echocardiographic scanning permits the differentiation of vegetations of bacterial endocarditis from valvular disease due to other causes. Two echocardiographic features are considered to be typical of aortic valve bacterial endocarditis. The first is the presence of thickened, uneven cusp echoes that can appear in systole or diastole alone, or less commonly, in both phases of the cardiac cycle. The second is the normal systolic excursion of all cusps regardless of their involvement in the disease process. Figure 2B contains features which were interpreted as aortic valve vegetations from bacterial endocarditis. A much larger experience will be needed accurately to assess the specificity of these echocardiographic features in characterizing aortic valve vegetations.

While correlations of the echocardiogram with the surgical or pathologic specimens have been good, the echocardiographic technique does have limitations. Lesions of 2 mm or less (1), lesions eccentrically placed on the aortic valve (1), and lesions on the left coronary cusp (11) may be difficult to visualize. Figure 2 demonstrates the final echocardiogram of this patient. While the correlation with the pathologic speciment is generally good, the small lesions on the mitral valve and the large left coronary cusp vegetation (Fig. 3) were not demonstrated echocardiographically.

Prolapse of aortic valve tissue into the left ventricular outflow tract (LVOT) has been reported in aortic valve endocarditis (4, 5, 7–14, 16). Diastolic echoes in the LVOT are said to represent prolapsing tissue. Figure 2A demonstrates diastolic echoes in the LVOT which were not present in earlier studies. These echoes were thought to reflect a flailing, torn cusp or a prolapsing valvular vegetation. The pathologic specimen displayed both features; it was not possible to state which caused the LVOT diastolic echoes. Echocardiography did not provide enough resolution so that the prolapsing structure could be specifically defined.

Serial echocardiograms of patients with aortic valve endocarditis yield important information that assists in the determination of the location, extent, and evolution of the disease. Serial echocardiograms have demonstrated an increase in valvular vegetation echoes after bacteriologic cure (1), the transition in one month from a thickened, vegetative valve to a flailing valve (8), and the disappearance of abnormal LVOT and aortic cusp echoes after a damaged valve was replaced with a prosthesis (10, 13). Roy and associates (12) described the disappearance of an abnormal mitral leaflet echo after a systemic embolic episode; the vegetation was found in a distant systemic artery. The present report demonstrates echocardiographically the transition from a normal to an abnormal aortic valve and LVOT in a case of bacterial endocarditis. Sixty-two days elapsed between the time the second and third echocardiograms were performed. More frequent studies might have displayed earlier stages of aortic valve disruption.

Acknowledgment

We would like to acknowledge Dr. Lotte Strauss for her interpretation of the pathologic specimens.

References

1. Dillon, J. C., Feigenbaum, H., Konecke, L. L. et al.: Echocardiographic Manifestations of Valvular Vegetations, Amer Heart J 86:698–704, 1973.
2. Feizi, O., Symons, C., and Yacoub, M.: Echocardiography of the Aortic Valve, Brit Heart J 36:341–351, 1974.
3. Martinez, E. C., Burch, G. E., and Giles, T. D.: Echocardiographic Diagnosis of Vegetative Aortic Bacterial Endocarditis, Amer J Cardiol 34:845–849, 1974.
4. Gottlieb, S., Khuddus, S. A., Balooki, H., et al.: Echocardiographic Diagnosis of Aortic Valve Vegetations in Candida Endocarditis, Circulation 50:826–830, 1974.
5. DeMaria, A. N., King, J. F., Salel, A. F., et al.: Echography and Phonography of Acute Aortic Regurgitation in Bacterial Endocarditis, Ann Intern Med 82:329–335, 1975.
6. Hirschfeld, D. and Schiller, N. B.: Echocardiographic Localization of Aortic Valve Vegetations, Circulation 49 and 50 (Suppl. III):III-143, 1974.

7. Giuliani, E. R., Roy, P., Tajik, A. J., et al.: Abnormal Echo in the Left Ventricular Outflow Tract in Bacterial Endocarditis, Circulation 51 and 52 (Suppl. II):II-69, 1975.
8. Wray, T. M.: The Variable Echocardiographic Features in Aortic Valve Endocarditis, Circulation 52:658-663, 1975.
9. Whipple, R. L., Morris, D. C., Felner, J. M., et al.: Echocardiographic Manifestations of the Flail Aortic Valve Leaflet Syndrome, Circulation 51 and 52 (Suppl, II):II-255, 1975.
10. Wray, T. M.: Echocardiographic Manifestations of Flail Aortic Valve Leaflets in Bacterial Endocarditis, Circulation 51:832-835, 1975.
11. Hirschfeld, D. S. and Schiller, N.: Localization of Aortic Valve Vegetations by Echocardiography, Circulation 53:280-285, 1976.
12. Roy, P., Tajik, A. J., Giuliani, E. R., et al.: Spectrum of Echocardiographic Findings in Bacterial Endocarditis, Circulation 53:474-482, 1976.
13. Yoshikawa, J., Tanaka, K., Owaki, T., et al.: Cord-like Aortic Valve Vegetation in Bacterial Endocarditis, Circulation, 53:911-914, 1976.
14. Wann, L. S., Dillon, J. C., Weymann, A. E., et al.: Echocardiography in Bacterial Endocarditis, New Engl J Med 295:135-139, 1976.
15. Estevez, C. M., Dillon, J. C., Walker, P. D., et al.: Echocardiographic Manifestations of Aortic Cusp Rupture in a Myxomatous Aortic Valve, Chest 69:685-687, 1976.
16. Lee, C. C., Das, G., and Weissler, A. M., Characteristic Echocardiographic Manifestation in Ruptured Aortic Valve Leaflet, Circulation 49 and 50 (Suppl. III):III-144, 1974.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

Eccrine Poroma of the Forehead

PHILIP LoBUONO, M.D., ROBERT KAHN, M.D., AND LEONARD V. KORNBLEE, M.D.

Abstract

Eccrine poroma, one of the sweat gland adenomas, is a benign, solitary tumor of the intradermal portion of the eccrine sweat duct usually found on the extremities. We present an unusual case of an eccrine poroma found on the forehead.

A case is reported of an eccrine poroma of the forehead that appeared clinically as an epidermal cyst. The tumor has not been reported before in this location and ordinarily is not considered in the differential diagnosis of solitary tumors of the face.

Eccrine poroma is a solitary, benign, superficial tumor of the epidermal appendages arising from the epidermal sweat duct unit (1).

Case Report

A 24-year-old Puerto Rican male presented himself to the Dermatology Clinic of The Bronx Veterans Administration Hospital with the complaint of a slowly enlarging, asymptomatic growth in the center of his forehead of approximately 1-year duration. On examination, a smooth, rounded, light brown elevation 1 cm in diameter was present in the center of the forehead. No similar lesions were noted elsewhere. A clinical diagnosis of epidermal cyst was made and the lesion was completely excised.

On histologic examination of the excised tissue (Fig. 1) there was visible a tumor mass originating in the epidermis and extending downward into the dermis as broad, anastomosing bands. The cells are rather uniform, cuboidal in shape, somewhat smaller than the malphighian cells and devoid of melanin granules; they have oval nuclei and are connected by intercellular bridges (Figs. 2 & 3).

These cells contain glycogen in their cytoplasm and are distase resistant.

Comment

This is the first report based on our review of the literature of an eccrine poroma being found on the forehead. Eccrine poromas are usually located on the extremities, although they have been reported on other areas. The predominant site is on the sole, as described by Pinkus in the original article (2). Eccrine poromas have also been reported on the palms (3), neck (4), chest (5), calf (6), scalp (7), and nose (8). Brownstein and Shapiro reported on the rarity of sweat gland adenomas. In a series of over 50,000 skin biopsies, only 0.4% were sweat gland adenomas; and, of these, 20% were eccrine poromas (9).

Histochemical staining of these tumors show them to have the same enzymes found in the eccrine sweat duct: amylophosphorylase, succinic dehydrogenase, and malic dehydrogenase. These findings support the hypothesis that these are really immature cells of the epidermal eccrine sweat duct (9).

From the Dermatology Section, Veterans Administration Hospital, Bronx, New York and Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Dr. Leonard V. Kornblee, Hospital, 130 West Kingsbridge Road, Bronx, N. Y. 10468.

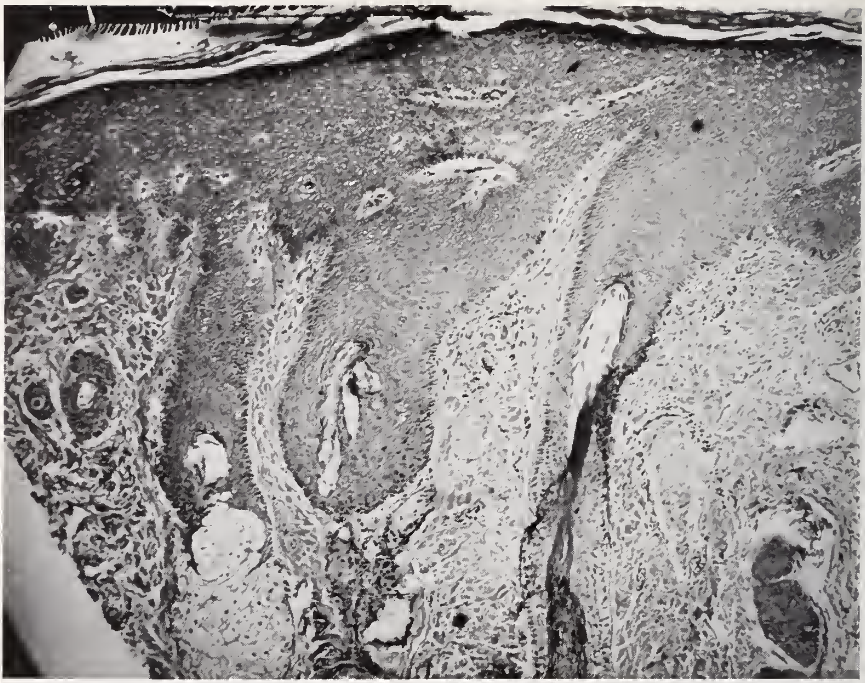


FIG. 1. Epidermal tumor mass extending down into the dermis (Hematoxylin-Eosin × 10).

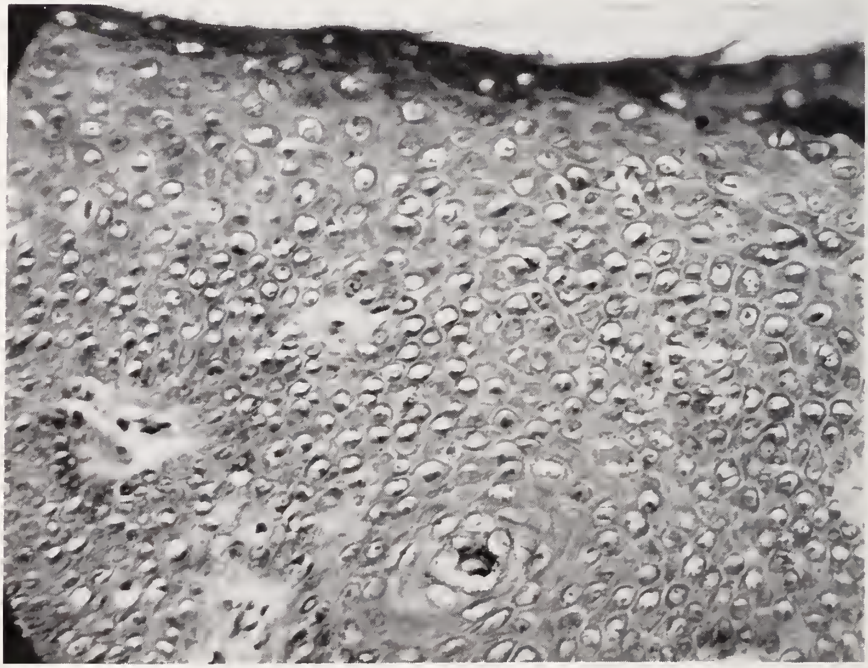


FIG. 2. Anastomosing bands of cuboidally shaped tumor cells (Hematoxylin-Eosin × 40).

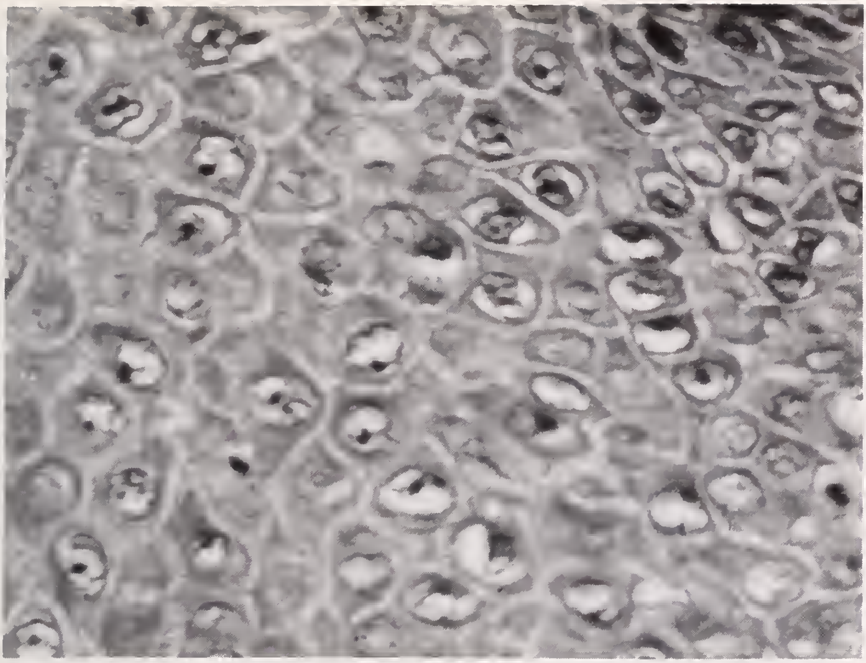


FIG. 3. Tumor cells showing cuboidal nuclei and intercellular bridging.

The differential diagnosis of eccrine poroma includes basal cell carcinoma, seborrheic keratosis, pyogenic granuloma, hemangioma, histiocytoma, Kaposi's sarcoma, epidermal cyst, neurofibroma, and amelanotic melanoma. This case reemphasizes that eccrine poromas can occur on the face and must be considered in the differential diagnosis of growing tumors on the face.

Acknowledgment

We wish to express our thanks to Dr. H. Choi of the Department of Pathology, Bronx Veterans Administration Hospital, for her assistance.

References

1. Montgomery, H.: Eccrine Poroma. In *Montgomery's Textbook of Dermatopathology*. Harper & Row. New York 1967, p. 892.
2. Pinkus, H., Rogin, J. R., and Goldman, P.: Eccrine Poroma: Tumors Exhibiting Features of the Epidermal Sweat Duct Unit, Arch Dermatol 74:511, 1956.
3. Hunter, G. A. and Hellier, F. F.: Tumors of the Palm and Sole Resembling Basal Cell Epithelioma, Brit J Dermat 72:283, 1960.
4. Okun, M. R. and Ansell, H. B.: Eccrine Poroma, Arch Dermatol 88:561, 1963.
5. Stritzler, C. and Stritzler, R.: Eccrine Poroma on the Calf of a Leg, Arch Dermatol 94:370, 1966.
6. Sanderson, N. V.: Eccrine Poroma. In *Rook's Testbook of Dermatology*. F. A. Davis Co. Philadelphia 1968, p. 1687.
7. Penneys, N. S., Ackerman, A. B., Indgin, S. N., and Mandy, S. H.: Eccrine Poroma: Two Unusual variants, Brit J Dermat 82:613, 1970.
8. Lever, W. F.: Eccrine Poroma. In *Lever's Histopathology of the Skin*. J. B. Lippincott Co. Philadelphia 1967, p. 573.
9. Brownstein, M. H. and Shapiro, L.: Sweat Gland Adenomas, Internat J Dermatol 14:397, 1975.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

The Mechanisms of Hemolysis in Wilson's Disease: Study of a Case and Review of the Literature

RICHARD J. MEYER, M.D. AND RALPH ZALUSKY, M.D.

Abstract

Wilson's Disease is a disorder of copper homeostasis classically characterized by hepatic, central nervous system, and renal dysfunction. The concept that hemolysis is an intrinsic part of hepato-lenticular degeneration has only recently been accepted. A 17-year-old girl with Wilson's Disease was studied during a phase of active hemolysis. Her red blood cell reduced glutathione content was low and had abnormal stability. Red cell enzyme activities were normal or increased, and hemoglobin stability, hemoglobin oxygen affinity, and red cell deformability were all normal. Copper-induced oxidative stress has been incriminated as the cause of hemolysis in Wilson's Disease, although supporting data is equivocal. In previous studies, supraphysiological copper concentrations added in vitro have been shown to affect G-6-PD, GSH and GSH stability with increased formation of Heinz-bodies. Both in this patient and in others reported in the literature these findings do not appear to adequately explain the degree of hemolysis observed. Copper-induced damage or alteration of the erythrocyte membrane requires further study.

Introduction

Wilson's Disease is a disorder of copper homeostasis characterized by hepatic, central nervous system, and renal dysfunction. The occurrence of hemolytic anemia in this disorder has been noted as early as 1936 by Sjovall (1) and in 1947 by Brinton (2). The concept that hemolytic anemia was an intrinsic part of the natural history of the disease was first proposed by Cartwright (3). Only recently has this concept been fully accepted (4-7).

An explanation for the mechanism of hemolysis in Wilson's Disease has been sought primarily through in vitro and retrospective studies (7-10). Owing to the transient nature of the hemolysis, and its appearance early in the course of the disease, few cases of acute ongoing hemolysis have been studied (4, 10, 11, 12). Results have often been inconclusive and in some cases, conflicting.

We have studied a patient during an acute hemolytic episode of Wilson's Disease. We report here our clinical and hematologic findings, and compare them with those cases previously described.

Case Report

A 17-year-old Puerto Rican girl came to the Mount Sinai Hospital because of increasing abdominal girth. The patient was first seen nine years earlier with a one-week history of abdominal distention. Physical examination at that time revealed an icteric girl whose liver

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From the Division of Hematology, Department of Medicine, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Richard J. Meyer, M.D., Department of Medicine, Berg Building, Room 359, Mount Sinai School of Medicine, Fifth Avenue and 100 Street, New York, N. Y. 10029.

and spleen were palpable 1 and 2 cm below the costal margins, respectively. There was no Kayser-Fleischer ring and the neurologic examination was normal. Hemoglobin was 8.7 gm%, white blood cell count 8,600/mm^3, platelet count 80,000/mm^3, reticulocyte count 8%, total bilirubin 7.6 mgm% with 6.6 mgm% conjugated, serum glutamic oxaloacetic transaminase (SGOT) 100 units, serum glutamic pyruvic transaminase (SGPT) 142 units, and Coombs test was negative. A diagnosis of Wilson's Disease was made on the basis of many ceruloplasmin assays showing less than 5 mgm%, and elevated urinary copper excretion. No further hematologic studies were performed at that time. The patient was started on penicillamine, 1 gm/day, and sulfurated potash. Over the ensuing years she did well with normal physical and mental development. Her liver function tests normalized. Hemoglobin ranged from 12.5 gm%–13.5 gm%, reticulocytes 1%, white blood cell counts 2,500–3,500/mm^3 and platelet counts 100–200,000/mm^3.

Nine months before the present admission, the patient discontinued her medications and was lost to follow-up. She was then readmitted with increasing jaundice. On physical examination she was icteric and both liver and spleen were enlarged 2 cm below the costal margins. A Kayser-Fleischer ring was present on slit-lamp examination. Her neurologic examination was normal. Hemoglobin was 10.0 gm%, white blood count 8,800/mm^3 and platelets 91,000/mm^3. The peripheral smear was normochromic, normocytic with polychromasia and basophilic stippling. There were no schistocytes or burr cells, but a few target cells were seen. Total bilirubin was 2.8 mgm%, haptoglobin 20 mg%, and reticulocyte count 10%. Direct and indirect Coombs test for IgG, IgM, IgA and complement components were negative, and fibrin split products were not present.

The patient's course was characterized by rapidly progressive hemolytic anemia, with reticulocyte counts rising to 36%, hemoglobin falling to 6.3 gm%, and bilirubin rising to a total of 30 mgm%, direct 26.1 mgm%. Beginning with the second week of hospitalization, she began to exhibit evidence of increasing hepatic insufficiency, with rising bilirubin and decreasing renal function. She ultimately succumbed to acute variceal bleeding. At postmortem examination she exhibited a 650 gm cirrhotic liver and a 450 gm spleen. Central nervous system examination was normal. The liver was not ashed for copper content.

Special Studies: Sugar-water test, osmotic fragility, Heinz-body preparation with and without acetylphenylhydrazine, hemoglobin electrophoresis, and determination of Hemoglobin F and A_2 were performed by routine methods[13]. Gluthathione and glutathione stability tests were performed according to the method of Beutler[14, 15]. Hemoglobin thermal stability[16], Glucose-6-phosphate dehydrogenase and pyruvate kinase assays were performed as previously described[17]. Hemoglobin P_{50} (18) and red cell 2, 3 DPG[19] were determined. Other red cell enzyme assays were performed by Dr. K. Tanaka using specimens of heparinized whole blood. The glycerol lysis time was performed by Dr. E. Gottfried on specimens drawn in EDTA.

To determine the effect of the patient's serum on normal red blood cells, incubation of her serum with type-specific donor red cells was performed at 37°C. Aliquots were removed for determination of GSH and GSH stability at 2, 3, 6 and 24 hours. Controls consisted of normal serum and red cells. Red cell filterability measurements were made using 5-micron Millipore (R) and 30-micron Nucleopore (R) filters at cell concentrations of 100,000 and 300,000 red cells/mm^3, and a negative pressure of 10 cm water. The time necessary for filtration of 10 ml of suspension was recorded.

Results

Hemoglobin electrophoresis showed a normal pattern and quantitation revealed 0.7% Hemoglobin F and 2.0% Hemoglobin A_2. The hemoglobin was heat stable. Osmotic fragility and 48-hour autohemolysis of the red cells were within normal limits. Glycerol lysis time was 57 seconds (normal 26-73 seconds). The sugar-water test for PNH was negative. The P_{50} value of whole blood was 31.5 mm Hg (normal 26.7 mm Hg) and the red cell 2, 3-DPG content 4.8 μMoles per liter RBC.

Red cell enzyme activities are shown in Table I. As might be expected with a young red cell population, most were elevated. GSH and GSH stability, on the other hand, were both reduced (Table II). Prolonged incubation of the patient's serum with normal red blood cells showed little change in the pattern of GSH levels as compared to the normal control (Table II). Red cell filtration studies are shown in Table III. The mean value for triplicate

TABLE I

Red Cell Enzyme Activities during Acute Hemolysis

Enzyme	Enzyme units (μMoles substrate utilized/10^{10} RBC/min)		
	Patient	Control	Normal Range
Glucose-6-phosphate dehydrogenase	5.74	1.98	2.65–3.89
6-phosphogluconate dehydrogenase	3.81	1.08	1.84–2.90
Glutathione reductase	4.86	3.68	2.00–3.59
Glutathione peroxidase	1.96	1.7	1.00–2.50
Hexokinase	1.03	0.19	0.21–0.32
Glucosephosphate isomerase	19.1	13.0	13.2–16.9
Phosphofructokinase	6.56	3.99	5.12–7.46
Aldolase	1.43	0.72	0.85–1.24
Triosephosphate isomerase	588	438	205.–239.
Glyceraldehyde-3-phosphate dehydrogenase	39.3	20.8	26.8–27.5
Phosphoglycerate kinase	44.9	38.9	39.3–51.3
2,3 mutase	9.4	6.10	6.01–9.99
Enolase	4.47	4.02	3.88–6.31
Pyruvate Kinase	12.3	5.8	4.03–6.49
Acetylcholinesterase	19.6	13.1	10.4–16.8
Transketolase	.30	.22	.22–.30
2,3 DPG mutase	.39	.30	.26–.56

TABLE II

Glutathione and Glutathione Stability Studies

Cells Studied	GSH (mgm%)	
	Before APH*	After APH*
RBC, normal (fresh)	72.6	68.7
RBC, patient (fresh)	51.2	31.0
RBC, normal + serum, normal (6 hrs, 37°C)	52.5	7.0
RBC, normal + serum, patient (6 hrs, 37°C)	53.7	7.2
RBC, normal + serum, normal (24 hrs, 37°C)	10.3	2.5
RBC, normal + serum, patient (24 hrs, 37°C)	4.7	0.2

* RBC incubated with acetylphenylhydrazine (APH) 100 mgm%, for 2 hours.

TABLE III

Red Cell Filtration Studies

Filter, type and pore size	Cell concentration	Filtration Time* (min)	
		Control	Patient
Millipore, 5μ	10^5	1:21.1	1:17.0
Nucleopore, 3μ	10^5	1:32.2	1:26.5
Nucleopore, 3μ	3×10^5	3:01.3	3:07:0

* Each value represents the mean of triplicate determination.

determinations showed no significant differences between the times of filtration for the patient's red blood cells as compared to normal controls.

Discussion

An animal model for copper-induced hemolysis exists in Australian "enzootic jaundice" of sheep. Sheep ingesting large quantities of copper remain well until they reach a critical hepatic copper content. At this juncture, they develop an acute hemolytic crisis, concomitant with evidence of hepatocellular damage. In man, with the ingestion of copper, either accidentally (20) or during suicide attempts (21), hemolytic anemia with hepatic malfunction and hypercupria ensue. In addition, acute hemolysis has been noted in patients with renal failure undergoing hemodialysis on units containing copper coils (22). Intriguing parallels exist between the above phenomena and the hemolytic anemia accompanying Wilson's Disease.

The pertinent clinical and hematologic findings in previously reported cases of hemolytic anemia associated with Wilson's Disease are shown in Tables IV and V. In all but one of the reported cases, hemolysis occurred as a presenting event with evidence of rapid copper flux manifested by extremely high urinary copper excretion, high serum copper, and, when measured, high red cell copper content (Table IV). All of the cases cited had hepatic malfunction at the time of hemolysis, ranging from increased direct-reacting bilirubin and "transaminitis" to frank hepatic failure. This most assuredly reflected a period of hepatic copper release (23).

It is often stated that the diagnosis of Wilson's Disease is preceded several years by an episode of hemolytic anemia with transient jaundice misdiagnosed as hepatitis (24). From our data it seems rather that hemolysis with hepatitis and copper flux is the presenting symptom of Wilson's and that a spectrum exists with any combination of degrees of hemolysis and hepatic destruction occurring. Whether a diagnosis of hepatitis or hemolysis is made depends upon which predominates. Hemolysis may be concealed by its low degree and anemia attributed to chronic disease with a relatively high direct-reacting biliruin further confusing the diagnosis. Seven of eight cases in the literature had predominantly direct-reacting bilirubin elevation despite fresh hemolysis (Table V). We believe that hemolysis occurred during the initial presentation of our patient, where the anemia and high reticulocyte count reverted following chelation therapy. Where sought, we believe that hemolysis will be found in each presentation of hepato-lenticular degeneration. Conversely, once a diagnosis of hemolysis or hepatitis is made, the diagnosis of Wilson's Disease should be excluded, as these findings are present in 90 percent of cases before neurologic disease is evident (Table IV). Hemolysis was self-limited in all surviving patients and prognosis depended on the extent of central nervous system or hepatic dysfunction.

The addition of increasing concentrations of ionic copper to red cells in vitro results in hemolysis. Although copper-induced oxidative stress of the erythrocyte has been incriminated as the etiology of the destruction (7), the site of such stress is unclear. Although reduced levels of glucose-6-phosphate dehydrogenase have been induced by increased copper concentration in both

TABLE IV

Clinical Findings in Reported Patients with Wilson's Disease and Hemolytic Anemia

Authors	Age at onset of hemolysis	Hemolysis present at diagnosis	Neurologic dysfunction	Hepatic dysfunction	Ceruloplasmin (mg%)	Urine Cu (mcg/24 hrs.)	Serum Cu (mcg%)
McIntyre et al (4)	12	Yes	No	Yes	51	2,541	103
	33	No	Yes	Yes	45	6,509	103
	9	Yes	No	Yes	32	2,391	420
Paswell et al (10)	8	Yes	No	Yes	6	292	420
Scheinberg et al (32)	16	Before	?	?	4.4		
	—	Yes	Yes	Yes	7.0		
Carr-Saunder et al (33)	10	Yes	No	Yes	5.0	3,000	
	7	Yes	No	Yes			
Brinton (2)	21	Yes	No	Yes			
	16	Before					
Cartwright et al (3)	8	Yes					
Deiss et al (7)	26	No	Yes	Yes	8.3	1,400–3,000	96
Iser et al (5)	27	Yes	No	Yes	14.5	2,237	122
	22	Yes	No	Yes	4.9	5,676	135
Slovis et al (34)	13	Yes	No	Yes	12	910	73
Turpin et al (35)	10	Yes	No	Yes		224	48
Walshe (6)	6	Yes	No	Yes			
Furrer et al (12, 36)	13	Yes	No	Yes			
	13	Yes	No	Yes	73	1,190	
Buchanan (37)	10	Yes	No	Yes	"18% of N"	Inc.	
	13	Yes	No	Yes	"15% of N"	Inc.	
Debray et al (38)	25	Yes	No	Yes		600	40
Wilms et al (11)	14	Before	No	?	16.5	337	46
	17	Before	No		10	350	90
	16	Before	No	Yes	14	500	132
	18	Before	No	Yes	3.5	700	90
Gruter (8)	20	Yes					
Warren (39)	7	Yes	No	Yes			

TABLE V

Hematologic Findings in Reported Patients with Wilson's Disease and Hemolytic Anemia

Authors	Hemoglobin (gm%)	Reticulocytes (%)	Haptoglobin (mg%)	Bilirubin Total/ Direct (mg%)	Comments
McIntyre et al (4)	12.8–5.5	1–18	0	18.0/	G-6-PD N[1]; Autohemolysis N
	14.0–9.7	1–6	20	2.8/	G-6-PD N; Autohemolysis N
	9.2–6.6	0–15	0	5.0/3.5	G-6-PD N; Autohemolysis N
Paswell et al (10)	5.5	18	0	3.8/2.4	G-6-PD D[2a]; Hexokinase, PK N
	10.2–7.2	7	0		
Scheinberg et al (32)	11.2–"42"				
	13.7				
Carr-Saunder et al (33)	"30%"	36		4.5/2.9	Autohemolysis N
Brinton (2)	"35%"	11			
	"70%"	6			
Cartwright et al (3)	4.4	24		7.0	
Deiss et al (7)	Hct 47–27%	16		0.8/0.4	Heinz Bodies increased after APH: Autohemolysis N: GSH Reductase N; G-6-PD N
Iser et al (5)	7.1	9			
	6.0	14			
Slovis et al (34)	"30%"	13			
Turpin et al (35)	RBC–1.82	13		1.4	
Walshe (6)	"90%–30%"				
Furrer et al (12, 36)	5.5	17		51/18	Autohemolysis N
Buchanan (37)	"20%"	24	26	3.4/1.0	G-6-PD N
	"22%"	22	33	13.3/6.8	
Debray et al (38)	RBC–1.3 $\times 10^6$/mm^3	27		8.2/4.7	
Wilms et al (11)	7.5	7.5	28	10.0	GSH–3010*
	7.8	8.0	0	2.3	GSH–1860
	4.5	2.6	0	15.0	GSH–2305
	6.8	8.6	0	4.4	GSH–1400
Warren (39)	7.2	Elevated			

* Micromoles/1 RBC, N = 2270 ± 300

[1] N = Normal

[2a] D = decreased

normal and Wilsonian red cells, in all but one report (40) these observations have been made at supraphysiological levels of copper (7, 20, 25, 9). Furthermore, these findings have not been substantiated *in vivo*. In only one instance was a decreased G-6-PD observed, while nine showed normal to increased levels during acute hemolysis (Table V).

The finding of reduced hexokinase, pyruvate kinase and 6 phosphogluconate dehydrogenase activity with in vitro addition of physiologic copper concentrations (40) has not been corroborated *in vivo*.

Decreased levels of reduced glutathione (26, 27) and glutathione instability (7) have been found in copper-treated red cells. Low levels of glutathione have further been found in sheep during their hemolytic period (28). The red cells of our patient showed a persistent reduction in glutathione, and a rapid fall of glutathione when exposed to the additional oxidative stress of acetylphenylhydrazine. Prolonged incubation of normal red cells with our patient's sera did not, however, produced a significant reduction of GSH and GSH stability as compared to controls.

As reduced glutathione serves a primary function in protecting the erythrocyte from oxidative injury, it would be tempting to propose that a copper-induced decrease of glutathione leads to hemolysis. Several points mitigate against this premise. First our case demonstrated only a 30% decrease in glutathione, insufficient by itself to account for the brisk hemolysis. Czlonkowska (9), in a study of 32 patients with Wilson's Disease, has describes similar decreases in GSH and GSH stability without evidence of hemolysis. Further, Smith (29) has described a reduction in GSH, GSH stability and Heinz-body production with acetylphenylhydrazine in ethanol-induced liver disease.

The other red cell enzymes measured during hemolysis were either normal or increased in activity. Unfortunately, superoxide dismutase has only been measured in one patient with Wilson's Disease; levels were found to be normal soon after an episode of hemolysis (30). It would be intriguing if further study showed decreased superoxide dismutate activity during hemolysis, as this enzyme system also serves in protecting the red cell from oxidative stress.

Hemoglobin becomes unstable in high copper concentrations as marked by decreased thermal stability (7) and increased Heinz-body production. Neither our case nor that of Wilms' showed changes in thermal stability during an actual hemolytic episode (18). Heinz bodies were not present in 8 of 8 cases measured. Only after incubation with acetylphenylhydrazine was a small increase found by Deiss (7) and ourselves. The production of Heinz bodies with acetylphenylhydrazine is more likely secondary to a decrease in the ability of the red cell to meet this oxidant stress rather than an inherent change in hemoglobin stability. Our patient did demonstrate a slight elevation of hemoglobin P_{50} in the face of normal 2, 3-DPG and acid base parameters. We cannot rule out the possibility that this represented a small copper-induced change in hemoglobin oxygen affinity.

Experimental evidence indicates that copper can alter membranes. Copper inhibits the transfer of glycerol into red cells, perhaps by membrane binding (4). Peroxidation of membrane fatty acids (27) and alterations in membrane-bound enzyme activity have also been noted (31). In our patient glycerol permeability as measured by glycerol lysis time, and red cell deformability were both normal. These are comparatively insensitive procedures and a more detailed analysis of membrane ef defects which may produce additional metabolic stress on the red cell may aid in explaning the onset of severe hemolysis.

References

1. Sjovall, E. and Wallgren, A.: Some Aspects of Heptolenticular Degeneration and Its Pathogenesis, Acta Psychiat Neurol 9:435, 1934.
2. Brinton, D.: Wilson's Disease, Proc Roy Soc Med 40:556, 1947.
3. Cartwright, G. E., Hodges, R. E., Gribler, G. J., Maloney, J. D., Daum, K., Wintrobe, M. M., and Bean, W. B.: Studies on Copper Metabolism XIII. Hepatolenticular degeneration. J Clin Invest 33:1487, 1954.
4. McIntyre, N., Clink, H. M., Levi, A. J., Cumings, J. N., and Sherlock, S.: Hemolytic Anemia in Wilson's Disease, New Engl J Med 276:439, 1967.
5. Iser, J. H., Steven, B. J., Stening, G. E., Hurley, T. H., Smallwood, R. A.: The Hemolytic Anemia of Wilson's Disease, Gastroenterology 67:290, 1974.
6. Walshe, J. M.: Wilson's Disease. The Presenting Symptoms, Arch Dis Child 37:253, 1962.
7. Deiss, A., Lee, G. R., Cartwright, G. E.: Hemolytic Anemia in Wilson's Disease, Ann Intern Med 723:413, 1970.
8. Gruter, W: Hamolytasche Krisen als fruhmanifestation der Wilsonschen Krankheit, Dtsch Z Nervenheik 179:401, 1959.
9. Czlonkowska, A.: A Study of Hemolysis in Wilson's Disease, J Neurol Sci 16:303, 1972.
10. Paswell, J., Cohen, B. E., Ben Bassat, J., Ramot, B., Shchory, M., and Lavi, U.: Hemolysis in Wilson's Disease. The Role of Glucose-6-Phosphate Dehydrogenase Inhibition, Isr J Med Sci 6:54, 1970.
11. Wilms, B., Blume, K. G., and Lohr, G. W.: Hemolytic Anemia in Morbus Wilson, Klin Wochenschr 50:995, 1972.
12. Furrer, H. V., and Tonx G: Die hamolytische Krise ben Morbus Wilson, Z Kinderheik 118:147, 1974.
13. Cartwright, G. E.: *Diagnostic Laboratory Hematology*. 4th ed. Grune and Stratton Inc. New York, 1968.
14. Beutler, E., Dixon, O., and Kelly, B. M.: Improved Method for the Determination of Blood Glutathione, J Lab Clin 61:882, 1963.
15. Beutler, E.: The Glutathione Instability of Drug Sensitive Red Cells. A New Method for the Determination in Vitro Detection of Drug Sensitivity, J Lab Clin Med 49:84, 1957.
16. Dacie, J. V., Grimes, A. J., and Meisler, A.: Hereditary Heinz-body Anaemia A Report of Five Patients with Mild Anaemia, Brit J Haemat 10:388, 1964.
17. Carson, P. E. and Preisler, H.: G-6-PD Deficiency, Am J Med 41:744, 1966.
18. Operator's Manual 1: 217 Blood Bank Laboratory. Instrumentation Laboratory IWC, 1972, pp. 7–9.
19. Meada, N., Chang, H., and Benesch, R. A Simple Enzymatic Method for the Determination of 2, 3 Diphosphoglycerate in Small Amounts of Blood, New Engl J Med 284:1239, 1971.
20. Fairbanks, V. K.: Copper-Sulphate Induced Hemolytic Anemia, Arch Int Med 120:428, 1967.
21. Chutani, H. K., Gupta, P. S., Gulati, S.: Acute Copper Sulphate Poisoning, Amer J Med 39:849, 1965.
22. Mangle, A. D., and Schreiner, A. W.: Induced Autohemolytic Anemia – A New Complication of Renal Dialysis, Ann Inter Med 73:409, 1971.

23. Goldfischer, S., and Sternlieb, I.: Changes in the Distribution of Hepatic Copper in Relation to the Progression of Wilson's Disease, Amer J Path 53:883, 1968.
24. Strickland, G. T., and Leu, M. L.: Wilson's Disease: Clinical and Laboratory Manifestations in 40 Patients, Medicine 54:113, 1975.
25. Metz E. N.: Mechanism of Hemolysis by Excess Copper, Clin Res 17:32, 1969.
26. Voegtlin, C., Johnson, J. M., and Rosenthal, S. M.: The Oxidative Catalysis of Crystalline Glutathione with particular Reference to Copper. J Biol Chem 93:435, 1931.
27. Moroff, G., Poster, J., Oster, G.: Enhancement of the Copper-Induced Hemolysis by Progesterone, J Ster Bio 5:601, 1974.
28. Todd, J. R. and Thompson, R. H.: Studies on Chronic Copper Poisoning. II Biochemical Studies of Sheep during Hemolytic Crisis, Brit Vet J 119:161, 1963.
29. Smith, J. R., King, N. E., Gottler, C. J., and Oski, F. A.: Abnormal Erythrocyte Metabolism in Hepatic Disease, Blood 4636:955, 1975.
30. Winterbourn, C. C., Hawkins, R. E., Brian, M., Carrel, R. M.: The Estimation of Red Cell Superoxide Dismutase Activity, J Lab Clin Med 85:337, 1975.
31. Bowler, K. and Duncan, C. J.: The Effect of Copper on Membrane Enzyme, Biochem Biphys Acta 196:116, 1970.
32. Scheinberg, I. H. and Sternlieb, I.: Liver in Wilson's Disease, Gastroenterology 37:550, 1959.
33. Carr-Saunder, E., Laurance, B.: Wilson's Disease Presenting as Acute Hemolytic Anemia, Proc Roy Soc Med 58:614, 1965.
34. Slovis, T. L., Thomas, K., Dubois, R. S., Reuben, S., Rodgerson, D. O., and Silverman, A.: The Varied Manifestations of Wilson's Disease, J Pediatr 7834:578, 1971.
35. Turpin, R., Caille, B., La Fourcade, J., Jerome, H., Boutelier, D., and Defranoux, A.: Hepato-Lenticular Degeneration and Hepatic Insufficiency Long Preceding the Neurological Symptoms, Ann Pediat (Paris) 10:277, 1963.
36. Tonz, G., Furrer, H. V., and Bangerter, U.: Copper Induced Hemolysis in Wilson's Disease, Schweiz Med Wschr 101:1800, 1971.
37. Buchanan, G. R.: Acute Hemolytic Anemia as a Presenting Manifestation of Wilson's Disease, J Pediat 8632:244, 1974.
38. Debray, J., Krulick, M., Blacher, R., and Dupuis, J.: Les disorders hematologiques au cours de la Maladies de Wilson, Ann Med Int (Paris) 122:737, 1971.
39. Warren, C. B., and Broughter, D. M.: Wilson's Disease, Arch Dis Child 37:242, 1962.
40. Boulord, M., Blume, K. G., and Beutler, E.: The Effect of Copper on Red Cell Enzyme Activities, J Clin Invest 51 459–461, 1972.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

Guidelines to Clearing Patients with Liver Disease for Surgery

SIDNEY LEIBOWITZ, M.D.

Introduction

The House Staff at Beth Israel Medical Center expressed the need for specific guidelines to assist them in their capacities as consultants to the surgical services in clearing patients with liver disease, or suspected liver disease, for contemplated surgery. Although specific guidelines to assist the Resident who serves in such consultant role actually do exist in the literature for other clinical areas (e.g., cardiac conditions) none existed for diseases of the liver insofar as I could ascertain. Therefore, I undertook to compose specific advice for use in this contingency. Once written it was received enthusiastically. It became apparent that other physicians might make use of them in similar problem situations.

In judging the fitness of patients with liver disease to undergo a surgical procedure one must basically take into account, as with any associated illness, the degree of urgency for the contemplated surgical procedure. Bearing this last factor in mind, we must assess either the significance of those findings in the patient which point toward hitherto unrecognized or undocumented liver disease involvement, or the extent and severity of the liver disease which is already diagnosed. In this light, let us approach the medical (liver) problem at the various levels.

I. *Finding of Chemical Abnormalities Only*

The patient has been in the hospital for a lesser or greater period of time while the surgeon has established the need to operate. He is ready to proceed to an operation and is puzzled by an elevated and unexplained SGOT (of 88). There is no history of recent liver disease or jaundice (or myocardial involvement or intramuscular injection). The medical consultant is called and must consider:

A. *Is this indicative of liver disease, recent or old?* Differential diagnosis will include consideration of:

1. Overlooked, additional data that may point to significant involvement of the liver, sufficient to warrant postponement of surgery pending deeper work-up and possibly seeking more expert opinion. Examples of such data include any or all of the following:

a. Hepatomegaly

From the Departments of Medicine and Ambulatory Health Services, Beth Israel Medical Center, New York, N.Y. 10003; and the Department of Medicine, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Requests for reprints should be sent to: Sidney Leibowitz, M.D. 325 East 16 Street, New York, N.Y. 10003.

b. Other clinical evidence of liver disease such as skin spiders, hint of icterus, accompanying splenomegaly, suggestion of ascites, pedal edema, clubbing of fingers, palmar erythema.

c. Laboratory data: borderline (or greater) elevation in serum bilirubin, bile in urine, elevated gamma globulin, elevated SGPT, elevated alkaline phosphatase.

d. Additional and possibly significant history which will warrant postponing surgery pending investigation, such as:

(1). Background of diabetes
(2). Obesity
(3). Background of recent significant fluctuations in weight, from previous obesity, with weight reduction programs, intermittently successful with resulting ups and downs in weight
(4). Employment of drugs in recent past, such as:
  Antibiotics (erythromycin estolate; tetracycline)
  Sulfonamides
  Isoniazid
  Tranquilizers (phenothiazines; librium)
  Anticonvulsants
  Laxatives (oxyphenysatin)
  Antithyroid drugs (thiouracil; tapazole)
  Antihypertensive agents (e.g., aldomet)
  Inhalational agents (halothane, penthrane)
  Steroid hormones, including testosterone and oral contraceptives
  Recognized potential hepatotoxins (e.g., organic arsenicals; carbon tetrachloride; methotrexate and other antineoplastic drugs; acetaminophen, cincophen; phenylbutazone, tolbutamide, chlorpropamide)

B. *Practical application of these findings:*

1. In the face of a deferrable surgical indication (= other than an emergency) the above additional findings should warrant the conclusion not to clear at once but to investigate further.

2. In the face of an urgent or emergency need to operate, the above type of findings need not deter clearance for surgery, particularly if they are *isolated* findings. However, pending further investigation postoperatively into the significance of such type isolated findings, all potentially harmful agents should be discontinued (e.g. sulfa drugs; testosterone; thorazine or compazine) for the immediate time period until the situation permits reassessment in studied fashion.

3. If the above findings, *in combination,* lead to a decision that a substantial set of evidence (clinical, historical, laboratory) has now been quickly adduced by the medical consultant (from reading the record *in full,* taking a detailed history from patient and family, and examination of patient) *pointing to recent, acute liver disease,* do not clear for surgery at this point unless the patient's life is definitely threatened more by a postponement than by immediate intervention.

Thus, under these circumstances, one would advise not operating unless the patient has an acute indication, such as recent perforated viscus or ruptured spleen.

Where the isolated laboratory finding is an elevated serum alkaline phosphatase or elevated serum bilirubin level (in the absence of biliuria or clinical jaundice) the same approach of chart analysis, history taking and careful physical examination is advised. If a ready explanation is found from these steps that tends to absolve the liver of significant involvement (for example, Paget's disease, in re the alkaline phosphatase or history of Gilbert's disease re the bilirubin), the patient's clearance should be weighed and decided in the light of the degree of urgency of the surgical need, and in most instances one would clear the patient.

If the situation is not thus reasonably comprehended and resolved, one would postpone surgery pending further investigation for most patients, excepting only those for whom demise is likely if surgery is not offered at once (see examples above) and also for those patients whose postponement would cause the loss of ideal time to intervene early (as with hip fracture).

II. *History of Prior Liver Disease*

A. History of past liver disease (hepatitis, cirrhosis, toxic hepatitis) *per se is not a bar* to proceeding to necessary surgery.

B. *If time had allowed,* a thorough workup before surgery should have ensued to permit you to judge the current activity of that disease, if still present.

C. *If the patient is newly admitted* and screening reveals no evidence of significant disease effects or activity (such as abnormal coagulation measurements; jaundice; high serum bilirubin or alkaline phosphatase or low serum albumin; hepatomegaly; skin spiders) the patient may be cleared for emergency surgery. Elective surgery should, in such cases, be preceded by the necessary baseline studies to permit judgment whether the past disease has current counterparts.

III. *Documented Evidence of Current Liver Disease (Acute, Subacute, Chronic)*

If the patient intended for surgery has clearcut evidence of liver disease currently, the patient's likeliest specific diagnosis must be understood and formulated, and then the reason for surgery aligned against those findings. Examples:

A. *Acute Viral Hepatitis*

1. No elective surgery should be permitted.
2. Serious need for (major) surgery (e.g. carcinoma of the gut) should be postponed as long as possible, awaiting subsidence of the acute hepatitis, allowing several months for the average severe case (much as one would advise postponement with recent acute myocardial infarction for three to six months).

3. Life-threatening (= immediate threat) illness, such as ruptured viscus or uncontrollable bleeding duodenal ulcer: operate as the "lesser of two evils," with care to avoid or promptly to overcome shock, hemorrhage, and potentially hepatotoxic anesthesia or antibiotics.

B. *Toxic Hepatitis, Acute*

Same as stated under "Acute Viral Hepatitis" with the additional guideline of eliminating and avoiding the toxin, if recognized.

C. *Cirrhosis of Liver, Compensated*

Indication for surgery should be judged on its own merits. Medical clearance, for all practical purposes, can rest on its degree of surgical need. Even elective surgery might be approved for most of such patients.

D. *Cirrhosis of Liver, Uncompensated*

The surgical procedure that one would approach here with greatest likelihood of medical clearance is that which is relatedly aimed at correcting accompaniments of the liver disease itself, such as portal hypertension (e.g., shunt surgery). This is always preferably performed as an elective procedure when the patient has been maximally prepared. The only time one clears for immediate surgery of this type is to stop variceal hemorrhage which is uncontrollable by other measures.

For unrelated surgery, the clearance should be withheld for elective surgery, carefully and individually considered for urgent surgery, granted for immediately life threatening surgery.

E. *Hepatic Effects of Cholelithiasis on Biliary Tract Disease*

When the presenting hepatic disease is secondary to the basic illness which surgery is intended to correct (e.g., pancreatic tumor or common duct stone or sclerosing cholangitis or tumor of hepatic duct), this is usually a thoughtfully considered, elective surgical approach and ordinarily does not demand *immediate* medical clearance as such. Actually, medical clearance is implicit (re the liver disease) in the indication for the surgery itself in the sense that cholangiohepatitis is minimized by relief of the bile-obstructing factor.

If the illness is a suspected liver tumor or granuloma, this is in the same zone as discussed above. Rarely should these situations present a problem in judgment for immediate clearance.

IV. *Role of Laparoscopy*

In some cases of planned surgery the state of the liver may be a decisive factor in whether, and how, to proceed surgically. (For example, when it is vital to know whether or not the liver is already metastasized from a suspected or diagnosed carcinoma of the colon.) Although this type decision is not exactly the same as "clearing" the patient for the operative procedure, it has somewhat similar implications because the degree of liver involvement may well determine the type and extent of the total surgical approach. In the workup of such cases, biopsy of the liver is generally of importance, but occasionally blind needle biopsy is either contraindicated or relatively hazardous (e.g., in the presence of coagulation defects; suspected liver abscess; right lower lung or pleural infection; massive ascites). In these circumstances, biopsy of the liver by direct inspection via laparoscopy is an informative procedure of merit which, in skilled and experienced hands, is performed with little or no morbidity.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

Medical Admissions from an Emergency Room: Factors Associated with Long Delays*

THOMAS A. REILLY, M.D., MICHAEL M. STEWART, M.D., M.P.H., JONATHAN M. METSCH, D.P.H. AND KENNETH C. FINE, M.D.

Introduction

The planning and evaluation of emergency medical services have received increasing emphasis since the passage of P.L. 93-154 (the Emergency Medical Services Act of 1973), and there has been growing attention to regionalization of services and with efficient and effective use of scarce health care resources. Research in emergency medical services (EMS) has proceeded rapidly in several different directions, with numerous reports focusing on specific subcomponents of the overall EMS system. Gibson has expressed concern with this fragmented approach (1), and has suggested that large-scale cooperative arrangements, such as interlocking trauma registries and cooperative reporting systems, should not become high priorities until existing EMS systems are more clearly understood and better methods are available for routine reporting and overall EMS evaluation. One of the most fundamental components of the EMS system, the emergency room itself, is an area in which further research clearly is needed.

The Health Services Research Unit of the Department of Ambulatory Care and Community Medicine, Mount Sinai Services, City Hospital Center at Elmhurst, is conducting a series of studies of patient care services within the emergency room of a large urban hospital. For example, a conceptual framework has been developed for planning emergency care services so as to maximize resource utilization by techniques of patient categorization and provider task analysis (2), and a new technique has been developed to monitor the flow of patients through the sequential stages of emergency room care (3). Specific emergency care problems have been studied in considerable detail (4), and patient flow patterns between the emergency room and OPD have been explored (5).

This report deals with the problem of long delays between emergency room arrival and hospital admission. Inpatient admission delays may be due to combinations of many different factors. Whatever the cause, extensive admission delays can be hazardous for all patients using an emergency room, leading to congestion, failures to identify changes in a patient's condition, delays in assessment of new patients entering the system, and creation of a more stressful working environment for emergency room staff. On the other

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From the Health Services Research Unit, Department of Ambulatory Care and Community Medicine, Mount Sinai Services, City Hospital Center at Elmhurst, Elmhurst, N. Y. 11373.

* Supported in part by a grant from The Commonwealth Fund

Requests for reprints should be sent to: Thomas A. Reilly, M.D., Department of Ambulatory Care and Community Medicine, City Hospital Center at Elmhurst, Elmhurst, N.Y. 11373.

hand, too brief a period of emergency room evaluation may lead to unnecessary or preemptive hospital admissions, causing substantial disruption to inpatient services.

A recent study was undertaken at City Hospital Center at Elmhurst (CHCE) to analyse admission delays from the emergency room, and to identify factors associated with unusually long delay times to admission. The results of this study show that admission delay times are surprisingly long and are significantly associated with medical problems which are not initially perceived by emergency room staff as well-defined or life-threatening conditions.

The Setting

City Hospital Center at Elmhurst (CHCE), an 850-bed municipal hospital affiliated with the Mount Sinai School of Medicine of The City University of New York, serves as the receiving hospital for a population of 800,000 persons in the western half of the Borough of Queens, New York City. The total annual visit rate for all emergency services is approximately 120,000, with approximately 65,000 visits to the adult medical-surgical Emergency Unit (EU). The EU is staffed at all times by 1–4 attending physicians and 3–6 members of the medical and surgical house staff. One attending physician is identified as the Supervising Physician for each eight-hour shift. The medical resident assigned to the EU serves as admitting physician to the medical inpatient service. Admitting physicians and consultants are on call for all other inpatient services. A nurse triage system, which refers patients with non-urgent problems to other areas of the hospital, is in operation 14 hours per day on weekdays and 8 hours per day on weekends. The EU has its own radiology suite, with technicians but without a radiologist at the present time. Simple diagnostic tests (CBC, urinalysis) are performed in an adjacent laboratory area. All other specimens are processed by main hospital laboratory.

Methods

This study focused primarily on patients admitted to the medical inpatient service during an eleven-day period in September–October 1975. There were 127 medical admissions during the study period, and 111 charts were available for review. Data were obtained on total delay time to admission, age, sex, presenting problem, admission diagnosis, prior contact with CHCE, prior hospital admission, and utilization of diagnostic and consultative services during the preadmission period in the EU. In order to compare delay times to admission, charts were also reviewed for 38 patients admitted to the surgical service and for 21 patients admitted to the orthopedic service on selected days during October 1975.

For purposes of this study, delay time to admission (DTA) is defined as the total time interval between initial arrival in the adult medical-surgical Emergency Unit (as stamped in the Emergency Unit chart) and the official time of hospital admission (as recorded in the Admitting Office registry).

Results

Table I shows the distribution of DTA for a total of 170 patients admitted to the CHCE medical, surgical, and orthopedic services. As shown, approximately 50% of medical and surgical patients included in this study were admitted in less than five hours. By contrast, approximately 80% of orthopedic admissions required less than five hours in the emergency room before hospital admission. The mean DTA does not differ significantly between the three groups.

For the 111 medical admissions included in this study, the mean DTA was 5.07 hours. Age and sex were not significantly correlated with length of DTA. Fifty-eight patients were female and 53 were male. Forty-two patients were under age 60, and 69 patients were age 60 or over.

The presence or absence of prior contact with CHCE was not associated with length of DTA. Sixty-seven patients were previously known to CHCE and 44 were new patients. Similarly, the total number of previous inpatient admissions to CHCE was not associated with length of DTA. Of 111 medical admissions, 73 were first admissions ever to CHCE.

The distribution of EU arrival times for the 111 medical admissions is shown in Table II, together with the mean DTA for all patients arriving in the EU during each four-hour period. Arrival times were not statistically associated with length of DTA.

Table III summarizes those aspects of emergency room care which were found to be statistically associated with length of DTA. As indicated in the left-hand column of the table, five presenting problems, four admitting diagnoses, and two types of consultations were statistically associated with a prolonged DTA. Conversely, patients with certain acute cardiovascular problems and with acute liver failure were admitted with a mean DTA which was significantly shorter than for the study sample as a whole. Both surgical and

TABLE I

Delay Times to Admission, by Service

DTA (hrs)	Medical		Surgical		Orthopedic	
	No.*	(Cum %)†	No.	(Cum %)	No.	(Cum %)
0–1	4	(4)	2	(5)	0	(0)
1–2	12	(14)	0	(5)	1	(5)
2–3	10	(23)	5	(18)	0	(5)
3–4	17	(39)	6	(34)	7	(38)
4–5	9	(47)	6	(50)	9	(81)
5–6	21	(66)	4	(61)	1	(86)
6–7	13	(77)	9	(84)	0	(86)
7–8	8	(85)	5	(97)	1	(90)
8–9	9	(93)	1	(100)	0	(90)
9+	8	(100)	0	(100)	2	(100)
Totals	111	(100)	38	(100)	21	(100)
Mean DTA	5.07		4.95		4.78	

* No. = Number of patients.

† Cum. % = Cumulative percent.

TABLE II

Emergency Unit Arrival Times for 111 Medical Admissions

Time of Day	No. of Patients	Mean DTA (hrs)
00–4	13	3.7
4–8	8	5.0
8–12	31	5.0
12–16	25	5.8
16–20	17	4.9
20–00	17	5.4
Total	111	5.07

TABLE III

Factors Associated with Prolonged DTA

Factors Significant (p value)	Factors Not Significant
Presenting problem	
alcoholism (.01)	Age
difficulty eating, drinking (.01)	Sex
ascites, edema (.01)	Prior CHCE contact
diarrhea (.01)	No. prior admissions
weakness, can't care for self (.05)	CBC
	Urinalysis
	SMA-6
chest pain (.01)*	Amylase
CHF, pulmonary edema (.01)*	Arterial blood gas
	ECG
Diagnosis	Chest x-ray
colitis, diarrhea (.01)	Abdominal x-ray
cardiac arrhythmia (.05)	Total no. lab tests
dehydration (.05)	Neurol. consultation
OMS, psychosis (.05)	Admitting service
	Time of EU arrival
acute liver failure (.01)*	
hypertension (.05)*	
Consultations Required	
social service (.01)	
surgery (.01)	

* Factors inversely associated with prolonged DTA.

social service consultations were associated with a prolonged DTA (see also Table IV).

The right hand column in Table III lists those factors not found to be statistically associated with length of DTA. However, utilization of diagnostic services by all patients in the study sample was very high (Table V), possibly masking the importance of the total utilization of laboratory and X-ray services as a factor contributing to the length of DTA.

Discussion

Delays in hospital admissions are inevitable in the emergency rooms of most large urban hospitals, particularly when the inpatient census is already

TABLE IV

Relation between Consultations and DTA

Consultations	No. of Patients	Mean DTA (hrs)
None required	73	4.50
Social service or surgery	19	7.02
Other	19	5.55
Total	111	5.07

TABLE V

Preadmission Utilization of Diagnostic Tests

Test	No. (%) of Pts.*
CBC	104 (94)
Urinalysis	23 (21)
SMA-6	101 (91)
Amylase	23 (21)
Arterial blood gas	40 (36)
Prothrombin time	42 (38)
ECG	68 (61)
Abdominal x-ray	24 (22)
Chest x-ray	89 (80)

* Many patients required more than one test.

high. The challenge is to identify those patients for whom eventual admission is delayed unnecessarily or for an unacceptably long period, and to take the necessary steps to reduce these admission delays. The stimulus to the present study was a documented complaint from the Department of Nursing regarding individual patients whose pre-admission stay in the EU exceeded eight hours. No data were then available on mean DTA by service, nor had a norm been established for a generally acceptable upper limit of DTA.

The results of this study, showing a mean DTA of 5.07 hours for medical admissions, were surprising and disturbing, and led to the introduction of a new administrative policy in the EU. Starting in late December 1975, the nursing staff routinely brought to the attention of the Supervising Physician any patient whose total stay in the EU had reached five hours. After assessing the patient's overall condition, the Supervising Physician was authorized to admit the patient directly to the hospital, if indicated. His other options were to give the physician managing the case one more hour to make a disposition decision or to discharge the patient from the EU. Under exceptional circumstances, the total six-hour limit could be waived entirely. It was hoped that this new policy would increase the sensitivity of all EU personnel to the need for more rapid evaluation and disposition of all patients, and that it would reduce the mean DTA for medical admissions.

Preliminary follow-up data for January–February 1976 do not indicate a statistically significant reduction in mean DTA for medical admissions, although the mean DTA has been lowered slightly under the new policy. Further studies are underway for more recent time periods.

The most important finding, in addition to the length of DTA, was the correlation of certain presenting problems with prolonged DTA. As indicated in Table III, patients presenting with alcoholism, anorexia, ascites, diarrhea and inability to care for themselves required significantly longer times in the EU. Many of these problems are nonspecific and often are not perceived by EU personnel as critical or life-threatening. The implication is that the less specific and less urgent a complaint, the longer it will take to reach a decision regarding admission.

Similarly, the association of social service consultation with prolonged DTA is probably due to the fact that patients requiring such consultations often present with ill-defined medical problems compounded or overshadowed by major social problems. In many instances, the decision to admit such patients is deferred until a thorough social service evaluation has been completed. This often reflects a tendency (particularly by house staff) to attempt to prevent hospital admission for patients whose social and personal problems appear more severe than their medical problems, and for whom it appears that adequate medical care could be provided in a less specialized setting.

The association of prolonged DTA with surgical consultations also merits comment. At CHCE, patients evaluated for possible surgical conditions are seen first by the surgical house officer in the EU, often followed by further consultations with more senior residents from the inpatient service. This hierarchical consultation system may contribute to the prolonged DTA for medical patients who also require surgical consultations before admission.

There is little comfort in finding that the number and types of diagnostic tests ordered in the EU are not statistically associated with length of DTA. As shown in Table V, utilization of diagnostic tests prior to medical admission is high, and probably excessive. A decision regarding admission may be postponed several hours while the physician awaits the results of laboratory tests. More judicious use of diagnostic tests and greater reliance on clinical judgment appears indicated in making decisions regarding medical admissions.

Follow-up studies of DTA for the period January–February 1976 confirm the statistical association between prolonged DTA and those presenting problems, admitting diagnoses and consultations shown in Table III. As these data are further refined, it is hoped that they can be used systematically as predictors of potentially prolonged DTA for patients whose likelihood of eventual medical admission is high. This will enable the Emergency Unit staff to expedite care for these patients on an individualized basis well in advance of the current administrative mechanism which becomes operative at five hours. Reduction of unnecessary delays between arrival and admission would be of direct benefit both to patients and to the Emergency Unit as a whole.

References

1. Gibson, G.: Emergency Medical Services: The Research Gaps, Health Services Research 9:6–21, 1974.
2. Metsch, J. M., Bassin, R., Stewart, M. M., et al.: A Conceptual Framework for Emergency Care Planning. J. Amer Coll Emerg Phys 5:782, 1976.
3. Fineberg, D. A. and Stewart, M. M.: Analysis of Patient Flow in the Emergency Room. Mount Sinai J Med 44:551, 1977.
4. Stewart, M. M., Harris, N., Greene, M. G., et al: Community Medicine Clerkships in an Applied Research Setting, J Med Educ 52:145, 1977.
5. Stewart, M. M., Metsch, J. M., Reilly, T. A., et al.: Patient Flow Modeling: a Practical Technique for Ambulatory Care Reorganization. Mount Sinai J Med 44:228, 1977.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

Analysis of Patient Flow in the Emergency Room*

DONALD A. FINEBERG, M.D. AND MICHAEL M. STEWART, M.D., M.P.H.

Abstract

The delivery of medical care in a hospital emergency room can be divided into a sequence of functional steps through which emergency room patients pass in reaching their eventual dispositions. This functional model provides the basis for an analytic method which can be used in describing and evaluating patient flow within a specific emergency room. The technique can be used to identify those factors which impede and facilitate patient flow, and to evaluate the probable effects of alterations in emergency room operations. Data are presented from the application of this method in a preliminary study conducted in the adult medical-surgical Emergency Unit at the City Hospital Center at Elmhurst, Queens, New York. It is likely that this simple and noninvasive technique will also be useful in other high-volume ambulatory care settings.

Introduction

In the last decade, increasing attention has been given to the role of emergency rooms in providing medical care. Emergency room (ER) visits account for five percent of all patient visits to physicians, and ER visits have more than quadrupled over the last fifteen years, a greater increase than that experienced by any other part of the health care system. In New York, the 15 acute-care municipal hospitals operated by the NYC Health and Hospitals Corporation currently account for approximately 50% of all ER visits. It would be valuable to have available some practical techniques for studying ER operations in such hospitals.

In this paper a general model of emergency room operations is presented. This model describes emergency room patient flow in terms of the functional steps through which patients pass while receiving care. This model can be used as the basis of a general analytic method for studying patient flow in the ER setting. The application of this technique of patient flow analysis is illustrated through the results of a small pilot study conducted at one large municipal hospital, City Hospital Center at Elmhurst. Conclusions are drawn regarding the usefulness of this patient flow model and the analytic method used to apply it in specific settings.

Patient Flow in the Emergency Room

People come to emergency rooms needing many types of care, and although it is important that emergency rooms always maintain the capability to manage life-threatening emergencies, many patients with less urgent problems must also be evaluated and treated. It is frequently not possible (or

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From the Department of Ambulatory Care and Community Medicine, Mount Sinai Services, City Hospital Center at Elmhurst, Elmhurst, N. Y. 11373; and Department of Community Medicine, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Requests for reprints should be sent to: Donald A. Fineberg, M.D., Department of Psychiatry, Yale-New Haven Hospital, New Haven, Ct. 06511.

* Supported in part by a grant from The Commonwealth Fund.

appropriate) to provide definitive care within an emergency room. Critically ill patients are admitted to the hospital for definitive care, and patients with less serious problems may require follow-up visits in other settings (clinics, doctors' offices). Thus the major operational goal of an emergency room is usually not complete treatment, but rather is appropriate patient disposition. In most emergency rooms, the following options exist for patient disposition: admission to hospital; discharge without follow-up; follow-up in the emergency room; referral to hospital outpatient department (OPD); and referral to personal physician. Some hospitals may also have short-stay admissions (48–72 hours) as a disposition option. Whatever the range of disposition options, an emphasis on disposition as an operational goal is critically important, since emergency rooms must constantly seek to expedite patient care and to avoid unnecessary congestion in order to preserve their capability to respond quickly to a sudden influx of patients with true emergencies.

The need to make rapid and appropriate decisions regarding patient disposition raises important questions when the ER is also used as a setting for medical training. Whether a patient is evaluated by an intern or by an attending physician may directly affect the speed and judgement with which a disposition will be made. For example, an intern may order numerous laboratory tests or specialty consultations in situations whereas an attending physician can make a rapid and appropriate disposition based on clinical judgment. The potential conflict between educational needs and patient care responsibilities, encountered so frequently throughout academic medicine, assumes special importance in the ER setting, where personnel must always be ready to meet unexpected demands for life-and-death care.

It is useful to view the primary activity of an emergency room as the functional process leading to disposition for all patients who enter the ER, no matter how urgent or nonurgent their problems. This process involves evaluation, medical or surgical intervention, and a disposition decision. The movement of patients through this process ("patient flow") will vary according to many factors, including numbers of patients, types of problems, ER staffing, and others. This paper presents a practical technique for studying patient flow in emergency rooms.

Patient Stations: A Conceptual Model

Studies of emergency room activities may be conducted for a variety of reasons, and it is unlikely that any single model of the ER "system" will be appropriate for all such studies. However, a general model describing patient flow, and delineating the functional steps involved in the flow, may be useful to a wide audience, either directly or as background information.

The emergency room "system," as the term is used here, refers to the internal operation of an emergency room, and more specifically to the organization and performance of the various sequences of tasks that are required to evaluate and manage many types of medical care problems. Thus the ER system described in this patient flow model is basically a queueing network within an emergency care setting, with different patients being processed through the system at differing speeds.

This ER queueing network can be thought of as having a number of "patient stations" at which patients receive particular components of their care. In a conceptual sense, every patient entering the ER progresses from one station to another, en route toward eventual disposition. A simplified version of this network, illustrating a typical emergency room, is shown in Figure 1, with the numbered boxes indicating the sequence of patient stations. A more detailed version is shown in Figure 2.

As shown in Figure 1, patients referred into the ER are triaged (sorted) by ER nurses or physicians, with room assignments depending on the type and severity of the condition. Patients remain in station 1 until this triage decision is made and implemented, at which point patients enter station 2. Each patient then undergoes initial physician evaluation, and remains in station 2 until this initial evaluation is completed. At this point x-rays, laboratory tests and/or specialty consultation(s) may be ordered, with the patient remaining in station 3X, 3L or 3C until the results are available to the ER physician. Patients are designated as being in stations 3X, 3L or 3C according to the relative importance of the awaited information in making a disposition decision. When these diagnostic studies are completed, patients must await the results of physician reevaluation (station 4). When reevaluation is completed and a decision has been made regarding disposition, patients are considered to be in station 5 until this disposition decision has been implemented and the patient physically leaves the ER.

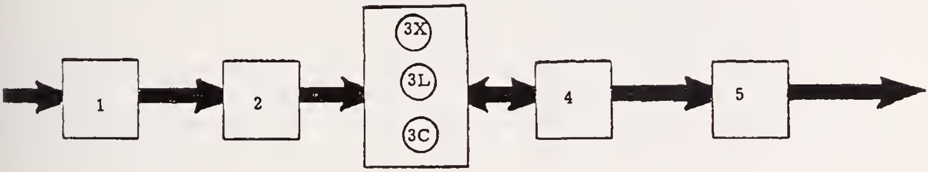

FIG. 1. Emergency room patient flow network. Boxes numbered 1–5 indicate the following patient stations: 1 = triage; 2 = initial evaluation; 3X = x-ray; 3L = laboratory data; 3C = consultation; 4 = reevaluation; and 5 = disposition.

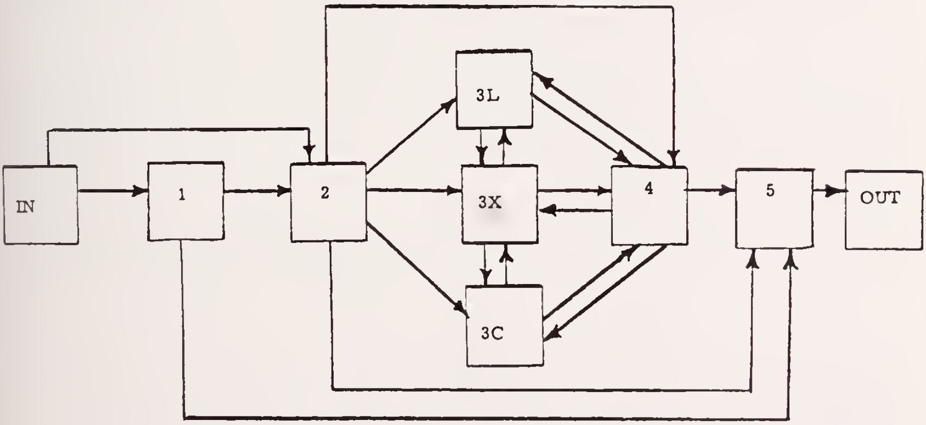

FIG. 2. Emergency room patient flow network (modified). Boxes numbered 1–5 indicate patient stations as shown in Figure 1.

Figure 2 is a modification of the same basic model, with the addition of a variety of alternate pathways showing the transit of individual patients through the various patient stations. Not all patients move through stations 1 to 5 in the same way. For example, patients arriving by ambulance from the scene of an auto accident may be immediately placed in a trauma room awaiting physician examination (station 2), with no need for initial triage within the ER (i.e., zero time spent in station 1). As another example, patients with minor, non-urgent problems may not require x-rays, laboratory tests, consultations, or reevaluation, and may move immediately from station 2 (awaiting completion of initial physician evaluation) to station 5 (disposition decision made, awaiting implementation). Another variation may occur when patients conceptually "move backward", for example from station 4 (awaiting or undergoing physician reevaluation) to station 3 (additional x-ray, lab tests or consultation required).

In a general conceptual sense, however, all ER patients move through these same five patient stations, although they may spend different lengths of time in different stations and may move through these stations in different sequences. These five patient stations thus represent mutually exclusive and mutually exhaustive functional steps in the process of ER care: every patient in the emergency room can be identified as being in one and only one of these stations at any given time. This general patient flow network and its breakdown into specific patient stations can obviously be further modified to suit particular emergency rooms, or for more detailed inquires related to the management of particular medical problems.

Several points regarding the various patient stations merit additional comment. Station 1 ("triage") refers to internal triage, or triage within the medical care area of the emergency room proper. Many hospitals also have operational procedures for external triage, that is, triage which determines whether patients will enter the emergency room at all or will be sent to non-emergency care areas. The schematic diagrams in Figures 1 and 2 do not include this external triage activity.

Patients in station 2 (awaiting or undergoing initial evaluation) are usually awaiting or undergoing medical assessment by a physician, whether intern, resident or member of the attending staff. Although there are now certain hospitals in which initial medical assessment (after internal triage) is performed by physician extenders, this arrangement is not yet widespread. In any case, the conceptual patient flow model remains the same regardless of who performs initial evaluation.

Patients are considered to be in station 3 while they are undergoing additional diagnostic tests, or while their physicians are awaiting the results of these tests. When the results of several different types of diagnostic evaluations are being awaited for a single patient (i.e., x-rays not yet ready, laboratory test results not yet available and consultation(s) not yet completed), a patient is clearly in station 3, but it may not be immediately apparent whether the patient should be classified as being in substation 3X, 3L or 3C. In actual practice, it is usually possible to determine which of the various items of information is most important to the requesting physician in making a disposition decision, and to classify patients accordingly. For example, if a patient is waiting both for an X-ray and a consultant, and if the consultant's opinion will be needed no matter what the X-ray shows, a patient is in station 3C.

It should also be noted that the figures do not include a station for patients who are undergoing or awaiting the results of treatment. This omission is intentional, as a simplifying device, and patients whose disposition depends on the response to medication or other therapy (i.e., patients being treated in the ER for asthma) can be classified in station 4 (if physical reassessment will be the next step after therapy) or in station 3L (if blood gases routinely will be drawn again). Similarly, patients requiring sutures may be placed in station 4, or, if a plastic surgeon must be summoned to do the suturing, in station 3C. However, it would be a simple matter to include in the model an additional substation 3T, and to classify in substation 3T those patients awaiting or undergoing therapeutic maneuvers which require substantial amounts of time, such as suturing, debridement, or a blood transfusion.

Patients classified in station 5 (disposition) are those for whom evaluation and therapy have been completed and a decision has been made as to where the patient goes next, although the patient is still physically present in the ER. Typical examples are patients awaiting transportation home, patients awaiting escort services for admission to the hospital, and patients awaiting availability of a bed in a special care unit.

It is important to understand that patient flow is an analytical construct of ER function, and not an overt activity to which patients can personally relate. While "moving" from station to station, a patient does not need to move physically (except perhaps to the x-ray department and back). For most patients, time spent with a physician is small compared to total time in the ER. Perhaps if patients were better oriented and more aware of where they were in the series of functional steps involved in their care, their personal experiences in the ER would be less distressing.

Finally, it must be recognized that the physical and organizational structure of emergency rooms is highly variable, and that even within a single ER, operating characteristics change with the time of day, the patient load, and many other factors. The conceptual model of successive patient stations may therefore require certain modifications to suit local characteristics. However, the principle underlying the model is generic to the operation of all emergency rooms: every patient who enters the ER is conceptually moving, through time, toward eventual disposition. The model provides a simple method for locating patients in their progress toward this disposition, for gathering data to evaluate ER function, and for identifying points where the patient flow process is congested or dysfunctional.

Applying the Model

The simplest and most direct method for studying patient flow through an emergency room is to determine the average elapsed time from patient entry to patient exit. This approach, although crude, may indicate substantial variations according to such factors as type of patient care problem, time of day, or staffing patterns. However, obtaining detailed data on total time in the ER by following individual patients through the system would require a one-on-one stop-watch approach that would be time-consuming, expensive and tedious. Furthermore, a person "clocking" patients during their time in the ER could directly affect the rate at which patients progress, by drawing special attention to these patients.

The conceptual model of successive patient stations can be used to study ER transit times without continuous monitoring of individual patients, and without affecting the rate at which patients progress through the system. This method involves counting, by direct observation, how many patients are in each patient station at successive time intervals. The distribution of patients by station at successive recordings produces a set of "system profiles" which shows how groups of patients progress through the ER system over a specific period of time.† Every observation produces a tally of patients in specific stations ("patient-stations"). For each individual patient, the number of patient-stations recorded in a given station is proportional to the time spent in that station. Similarly, for each station, the number of patient-stations recorded is proportional to the time spent in the station by all patients included in the study. Thus, by periodic counting of how many patients are found in each of the ER stations, it will be possible to make statements of the following type:

1) on the average, patients in the ER spend X% of their time waiting for laboratory tests (station 3L).
2) at any one time, on the average, Y% of patients in the ER are waiting for consultations (station 3C).
3) patients being admitted to the Coronary Care Unit from the ER wait an average of Z minutes for actual admission, after the decision to admit to this Unit has been made (station 5).

From a methodologic viewpoint, periodic counting of patient-stations (specific patients in specific stations) permits the use of proportionality in estimating how long patients spend in the different stations. Suppose, for example, that ten successive hourly counts were made of all patients physically present in the ER, and that the proportions of all recorded patient-stations were as follows:

Station	*% of Patient-Stations*
1	8%
2	12%
3	40%
4	28%
5	12%

As an approximation, it could then be said that patients in the ER during the period of observation spent 40% of their total ER time waiting for the results of diagnostic information not obtained during initial evaluation (station 3, including 3X, 3L and 3C).

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† This method is analagous to studies of highway traffic which rely on successive aerial photographs to indicate patterns of traffic flow and points of congestion.

The analytic method afforded by application of this patient station model has a number of more sophisticated extensions. For example, it is possible to determine what types of patients or patient care problems are "trapped" in certain patient-stations. It is also possible to study whether flow time through successive patient stations is related to patient arrival rates during specified time periods. In addition, the time course of high frequency, rapid flow problems (e.g., minor trauma) can be compared to that for low frequency, slow flow problems (e.g., severe abdominal pain). This is important in terms of ER resource utilization, since the "incidence" of presenting problems may be less important than their "prevalence," and total time in the system and total resources invested in emergency room management may be more closely related to total time in the system (total number of patient-stations per patient) than to the acutal number of individual patients presenting with any given problem. Patients presenting with coma, for example, might represent 1% of all ER visits but account for 5% of all time spent by patients in the ER.

From an operational perspective, the most important aspect of studying patient flow with this analytic method may be the opportunity to identify those groups of patients whose total time in the ER is prolonged by factors that can be modified by changes in ER policies and procedures.

Pilot Study of Emergency Room Patient Flow

On February 20, 1975, the patient station model was used to study patient flow in the adult medical-surgical Emergency Unit at City Hospital Center at Elmhurst, an 850-bed municipal hospital in the northwestern section of the Borough of Queens, New York City. Data were obtained by direct observation by the senior author for ten approximately evenly-spaced system profiles during the period 10 a.m.–11 p.m. Data collection for each system profile required approximately 20 minutes. Table 1 summarizes the data collected on 93 individual patients during these ten successive system profiles.

The summary column at the right of Table I (Patients per Profile) shows that the number of patients counted as physically present in the ER during each profile varied from a low of 10 to a high of 28. The summary row at the bottom of Table I (Station Totals) shows the distribution of patient-stations by station during the period of the study. These data can be converted into percentage totals to indicate what proportion of total patient time in the ER was spent in each.

Station	1	2	3X	3L	3C	4	5
% of Total ER time	7	22	19	5	7	30	10

These estimates of percentages of total patient ER time spent in each station can be adjusted in order to examine the experiences of specific patient groups. For example, all patients in this study did not require x-rays, and the 19% of total patient time spent in station 3X was accounted for by only 51% of all patients. Thus, for patients who did require x-rays, the per cent of their total time spent in station 3X can be calculated separately. Similar reasoning can be applied to all other stations.

TABLE I

*Emergency Room System Profiles, Elmhurst**

		Stations							Patients/Profile
		1	2	3X	3L	3C	4	5	
System Profile Number	1	1	6	3	0	1	2	0	13
	2	0	1	4	0	1	7	1	14
	3	1	5	1	3	1	2	2	15
	4	2	6	2	1	4	7	0	22
	5	1	3	5	1	2	7	3	22
	6	0	3	3	1	2	6	2	17
	7	0	1	0	0	0	7	2	10
	8	2	2	1	1	0	3	1	10
	9	4	7	9	1	0	5	2	28
	10	0	2	3	0	1	3	2	11
Station Totals		11	36	31	8	12	49	15	162 Total Patient-Stations

* N = 93 patients.

Since each patient's ER chart was stamped with the time of arrival, it is also possible to examine how progress through successive stations is related to total elapsed time in the ER. Table II summarizes this information for all 162 patient-stations recorded for 93 patients. As shown, 34 of 162 patient-stations (21%) were recorded for patients who had been in the ER more than three hours. These 34 patient-stations were recorded in stations 3L, 3C, 4 and 5, with 17 of 34 of these patient-stations (50%) found in station 4 (patients awaiting reevaluation). Thus patients awaiting reevaluation accounted for approximately half of all patient time spent in the ER beyond three hours.

Referring again to Table II, the 11 patient-stations recorded for patients who had been in the ER for more than five hours were attributable to nine individual patients. The functional path followed by each of these nine patients, in terms of their stations during successive system profiles, can be readily reconstructed to assist in an analysis of the factors contributing to their long stays in the ER (some patients underwent long periods of reevaluation, some required repeat laboratory tests, x-rays or consultations, and some spent long periods of time awaiting transportation home).

Studies of patient flow can be used as a mechanism for quality control, provided that criteria external to the ER system are made explicit. For example, an emergency room staff may decide that three hours is the acceptable upper limit for total time from ER arrival to implementation of disposition. Patient flow data can then indicate the extent to which this goal is being achieved, as well as the relative time contribution of various ER functions. The decision as to acceptable total time for the average patient in the ER is, of course, completely independent of the method for studying patient flow.

Considerable refinement of this patient flow method is possible, and indeed such refinement will be necessary if serious on-going research is to be

TABLE II

Time in the Emergency Room by Patient Station

		Station							Total
		1	2	3X	3L	3C	4	5	
Elapsed Time in the ER (hours)	0–1	10	30	11	1	1	5	1	59
	>1–2	1	4	12	1	3	16	2	39
	>2–3	0	2	8	2	4	11	3	30
	>3–4	0	0	0	2	0	6	5	13
	>4–5	0	0	0	1	1	6	2	10
	>5	0	0	0	1	3	5	2	11
Total		11	36	31	8	12	49	15	162 Total Patient-Stations

undertaken. However, as a practical operational technique for monitoring overall ER function and for identifying problems in the process of ER management, application of the patient station model has the advantage of being conceptually straightforward and relatively simple to use. This technique for patient flow analysis merits further serious consideration.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

Trends in the Demand for Emergency Room Services: The Mount Sinai Hospital

ROGER GLASS, M.D. AND DAVID FRIEDMAN, M.S.

Introduction

A rational approach to the provision of emergency room care can be achieved only after trends in the demand for these services have been documented. Registration data for emergency room visits used heretofore only for billing has been reprogrammed to evaluate long and short-term trends in the utilization of services. Seasonal, weekday, hourly, and age-related trends in the demand for services underline some current problems in staffing. More sophisticated use of this billing data in the future may provide a basis for understanding the use of outpatient services by selected subgroups of patients (new patients, geriatric patients, repeaters and high utilizers) and the flow of patients through the clinic system.

Setting

The Emergency Room of the Mount Sinai Hospital operates nonstop year-round. Medical care is delivered by the house staff in medicine, surgery, and pediatrics. Psychiatric services are administratively separate and are not included in this report. The patients arrive on their own and the hospital has no regular relationship with an ambulance service, a practice that minimizes the volume of true emergencies. Between 8 AM and midnight, all patients under 20 years of age are seen in a pediatric walk-in clinic. During the same hours, adult patients are triaged by nurses either for medical or surgical care. Between midnight and 8 AM, all patients, regardless of age, are cared for in the medical area.

Methods

For purposes of billing, data on every patient entering the emergency room is registered in a computerized file. This record includes the patient's name, address, unit number, sex, age, pay status, and time and date of registration. Access to this data has been facilitated by a new computerized management system called RAMIS (Rapid Access Management Information System). This system allows the user to abstract, edit, and analyze data already present in the main billing file. Since September 11, 1976, all emergency room visits have been abstracted from the billing files and this report represents our first analyses of the 17,886 visits in the subsequent two-month period. Some

From the Departments of Medicine and Ambulatory Care of Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Roger Glass, M.D. Bureau of Epidemiology, Center for Disease Control, Atlanta, Ga. 30333.

historical data from the annual reports of the emergency room are included in this study to place our current data in perspective. Adult visits include both medical and surgical patients seen between 8 AM and midnight who are more than 19 years old and patients of all ages seen between midnight and 8 AM. Night visits have been considered adults since there are relatively small numbers and most patients are in the adult age range.

Results

1) *Long-term trends:* Over three of the past four years for which comparable data are available there has been a 3.1% per year increase in the demand for all emergency room services. This increase was due predominantly to an increase in adult patient visits (Table 1). In 1976, this trend was reversed, in part due to an 8-day strike by hospital employees which caused a 9% decline in visits in the 3rd quarter (1). Adult patients outnumber pediatric cases almost two to one. The monthly trend in the number of emergency room visits for adults and pediatric patients is quite distinct (Fig. 1). Pediatric visits are greatest in the winter months, lowest in the summer months, and intermediate in both spring and fall. Adult visits are greatest in the late summer and early fall and lowest throughout the winter except for January.

TABLE I

The Demand for Emergency Room Services: 1973–1976

Year	Pediatric	(% Δ)	Adult	(% Δ)	Total	(% Δ)
1973	32,820		54,402		87,222	
1974	33,297	1.5	56,598	4.0	89,895	3.1
1975	33,498	0.6	59,312	4.8	92,810	3.2
1976	34,899	4.2	57,249	−3.4	92,148	−0.7

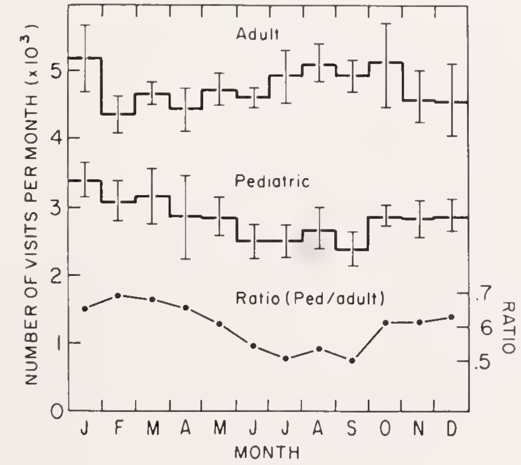

FIG. 1. Number of Emergency Room Visits by Month: 1973–1976.

2) *Short-term trends:* There are large daily variations in number of patients seen in the emergency room (Fig. 2). The large standard deviation indicates that large variations in the number of visits can be expected. Statistically, differences of one standard deviation from the mean will occur on three days in ten. Much of this variability can be explained in terms of weekday trends. The number of visits peaks on Mondays and decreases significantly and almost continuously until the weekend (Fig. 3). Approximately 100 more patients are seen on Mondays than on Sundays, representing a 42% day-to-day difference.

For adults, registration is greatest in the morning hours and decreases slowly during the day (Fig. 4). For pediatrics, the flow is more continuous with a mid-afternoon rise. The peaks at 9 AM and 4 PM represent periods when the registration personnel change and registration times may be delayed.

3) *Demographic Parameters: Age and Sex.* 28% of all patients seen in the emergency room in the period of this study were less than 10 years of age and 10% of all patients were 60 or more (Fig. 5). Excluding children under 10,

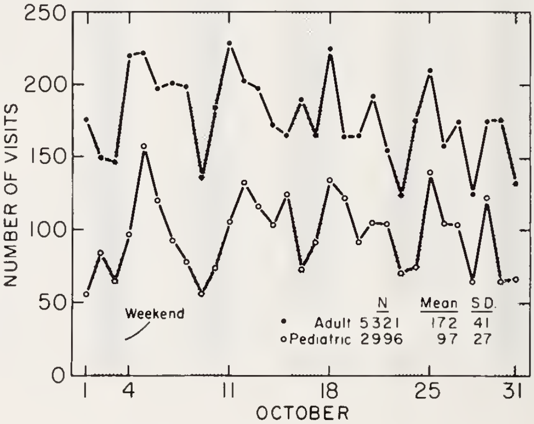

FIG. 2. Emergency Room Visits: October 1976.

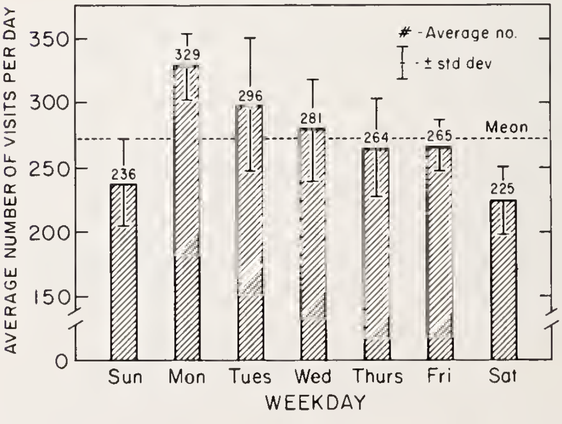

FIG. 3. Emergency Room Visits by Day of Week (September 11–November 15, 1976 – 17,886 visits).

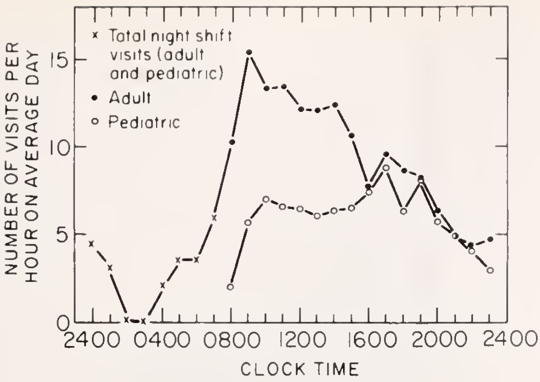

FIG. 4. Emergency Room Visits by Hour (October 1976).

female visits outnumbered male visits in every age group with 3 females registering for every 2 males.

Geographic Location. Analysis of patient zip codes indicates that the emergency room provides its services primarily to local residents (Fig. 6). 90% of all visits come from the boroughs of Manhattan and the Bronx and 67% come from areas within the zip code area of the hospital itself or an immediately adjacent zip code area.

Payment Status. Medicaid and self-pay patients are almost equally represented among emergency visitors (43% and 46%, respectively), and Medicare patients (5%) and patients with other means of payment (6%) account for the remaining groups.

New Registration. 40% of emergency room patients are introduced to the hospital through this facility. The remaining 60% of patients had been previously registered with the hospital or clinic.

Discussion

Patterns of emergency room visits over time have been studied in many institutions and vary with the local situation (2-4). In all studies and in the inner city areas in particular, the rapid growth of visits has been associated with the changing role of the emergency room—from a facility for true emergencies, to a community walk-in clinic. Several trends in this billing data are consistent with this change. Studies from the City Hospital Center at Elmhurst of emergency room utilization for urgent and nonurgent cases indicate that the nonurgent cases cluster to the convenience hours—weekdays, particularly Mondays, and to the working hours of 9 AM-5 PM; urgent cases are more uniformly spread throughout the week and the working hours (5). The non-urgent pattern is observed in the present study; the large number of visits on Mondays and Tuesdays and after 9 AM is consistent with medical compliants which are annoying but for which acute medical care has already been deferred by the patient. For 40% of the patients studied, the emergency room served as the first point of contact between the patients and the clinic system. In the absence of a walk-in clinic or other setting to allow for easy access to the clinic system, the emergency room fulfills much of this

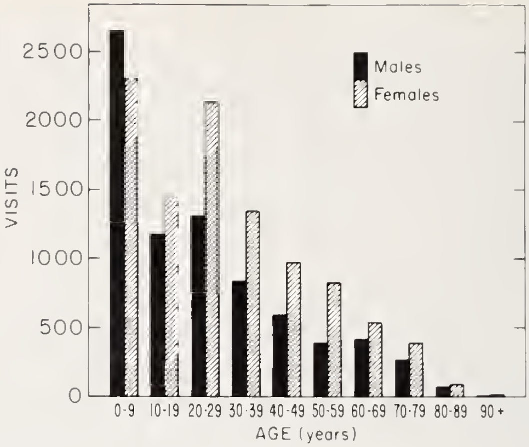

FIG. 5. Distribution of Emergency Room Visits by Age and Sex (September 11–November 15, 1976 – 17,886 visits).

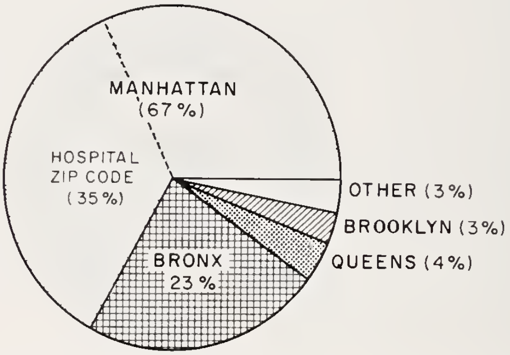

FIG. 6. The Distribution of Emergency Room Visits by Borough (September 11–November 15, 1976 – 17,886 visits).

role in screening new patients with nonemergent complaints.

The walk-in clinic function is recognized in pediatrics. All pediatric emergency room visits are treated under the rubric of pediatric ambulatory care. The 50% higher rate of medicaid reimbursement for clinic visits versus emergency room visits makes this a financially profitable incentive for the institution. Establishing a medical walk-in clinic for patients with nonemergent problems would allow emergency room physicians to deal more effectively with true emergencies. A well-run medical walk-in clinic could give a vital triage function to the clinic system while caring for patients with nonurgent problems.

The present analysis has attempted to identify trends in the demand for emergency room services which could be met with the more rational allocation of professional and nonprofessional staff. Increased demand for services occurs in the months of July to October and January, on Mondays and Tuesdays, and in the working day hours of 9 AM-4 PM. The scheduling of emergency room staff, their numbers, hours, and vacations should reflect these trends in the community's demand for services.

The present study is based entirely on data collected for billing in a system organized to monitor reimbursement. Little emphasis has previously been placed on the utilization of this data to improve patient care. In this study, we have identified trends in the demand for emergency room services using the simplest registration information so that staffing patterns can be based on hard data. The computer program developed will provide updated reports of the demand for emergency room services so that staffing patterns can be periodically reviewed.

The ease with which a large volume of billing data can be accessed with the RAMIS system has encouraged us to go on and examine several special emergency room problems. A monthly printout of repeat visitors might help identify a group whose care could be provided with more continuity in the clinic. Patients receiving new registration numbers who have nonurgent complaints could be directed to a walk-in clinic which would serve a screening function and provide better follow-up. Evaluation of the patterns of emergency room use by patients over 65 might identify a group suitable for a geriatric clinic or home care program. Since all out-patient billing data is potentially available, patients seen in the emergency room and referred to a specific clinic for follow-up could be traced to evaluate the degree of compliance with appointments for patients with different complaints. Billing data is not optimal to study many problems in outpatient medicine but it can provide some basic data important to increasing our understanding and to improving our approach to delivering quality ambulatory care from the hospital setting.

Acknowledgment

The authors wish to thank Mr. Walter Trogg for his help in data processing and programing.

References

1. Levenson, B. and Mailick, D.: Third Quarter Report, Division of Ambulatory Care, Prepared by the Office of Applied Social Research, Department of Community Medicine, Mount Sinai School of Medicine of The City University of New York, 1976.
2. Torrens, P. R. and Yedvab, D. G.: Variations among Emergency Room Populations: A Comparison of Four Hospitals in New York, Med Care 8:60, 1970.
3. Noble, J. H., et al.: Variations in Visits to Hospital Emergency Care Facilities, Med Care 9:415, 1971.
4. King, B. G. and Sox, E. D.: Emergency Medical Service System: Analysis of Workload, Publ Hlth Report 82:995, 1967.
5. Stewart, M. M. and Reilly, T.: An Analysis of Patient Flow in the Diagnostic Walk-in Clinic at Elmhurst General Hospital (Unpublished data).

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

PEDIATRIC NOTES

AARON R. RAUSEN, M.D., EDITOR

Diabetes Mellitus and Congenital Rubella: Report of a Case

Submitted by

EDITH P. HALVORSON, M.D.

Since Hay first described a patient with diabetes mellitus in association with congenital rubella in 1949 (1), many other cases have been reported in the literature (2-5).

Forrest et al found 5 patients with diabetes mellitus and 4 with latent diabetes among 44 young adults with congenital rubella. This incidence—20%—suggested a causative relationship between these conditions (5).

The case to be reported documents yet another child with congenital rubella who manifested diabetes mellitus, further supporting the causal relationship between the two conditions.

Case Report

L. V., a Hispanic male, was born at term to a 20-year old primigravida who denied any disease or complications during pregnancy. Birthweight was 2510 grams and Apgar scores at one and five minutes were nine. The neonatal period was uneventful except for some feeding difficulty during the first month of life. A cardiac murmur, characteristic of pulmonic artery stenosis, was detected at eight months of age. At 12 months of age profound bilateral sensory neural deafness was noted which has been partially corrected by hearing aids. Rubella antibody titers at this time were positive at 1:32 and 1:64 dilutions in the mother and child respectively. The child has remained below the third percentile for height and weight. A right hydrocele repair was performed at four years of age.

At seven years of age polyuria, polydipsia, polyphagia, and loss of weight developed. The urine was markedly positive for glucose and acetone. A fasting blood sugar was 443 mg%. The child was hospitalized and stabilized so that on discharge his diabetes mellitus was controlled on 6 units of NPH insulin per day. The child was found to type HLA2, A3, B5 and BW40.

Family history is significant in that the paternal grandmother and an aunt, the maternal grandfather and his aunt, all presented with late onset diabetes.

Discussion

Although the patient has a family history of diabetes, appearance of this complication early in life might be attributed to his congenital viral disease. Rubella virus can affect the interstitial and periglandular tissue of the fetal pancreas (6); this may represent the pathogenetic basis for the development of

From the Department of Pediatrics, Beth Israel Medical Center, New York, N. Y. 10003.

Requests for reprints should be sent to: Edith P. Halvorson, M.D. Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, N. Y. 10003.

pancreatic insufficiency in one case reported by Donowitz and Grybowski (7). On the other hand the high incidence of diabetes mellitus reported in children and young adults with congenital rubella (5) suggests that the virus also can affect islet cell function. Johnson et al (4), discussing two cases of diabetes mellitus in children with rubella syndrome, speculate that this condition may be attributed to a reduction in the number of beta cells of the pancreas or else to the cytolytic action of the rubella virus in the form of immunologic or direct vascular damage to the islets of Langerhans, both mechanisms interfering with the production of insulin.

Menser et al (8) reported recently an increase in the frequency of antigen HLA8 in patients with congenital rubella who developed diabetes, implying genetic predispositional factors. In the case presented, HLA8 antigen was not present.

Summary

A case of a child with congenital rubella syndrome with deafness and congenital heart disease who developed diabetes mellitus at the age of 7 years is presented, further supporting a possible causal relationship between the two conditions.

References

1. Hay, D. R.: The Relation of Maternal Rubella to Congenital Deafness and Other Abnormalities in New Zealand, New Zealand Med J 48:604, 1949.
2. Forrest, J. M., Menser, M. A., and Harley, J. P.: Diabetes Mellitus and Congenital Rubella, Pediatrics 44:445–447, 1969.
3. Plotkin, S. A. and Kaye, R.: (Letters) Diabetes Mellitus and Congenital Rubella, Pediatrics 46:650–651, 1970.
4. Johnson, G. M. and Tudor, R. B.: Diabetes Mellitus and Congenital Rubella Infection, AMER J Dis Child 120:453–455, November 1970.
5. Forrest, J. M., Menser, M. A., and Burgess, J. A.: High Frequency of Diabetes mellitus in Young Adults with Congenital Rubella, Lancet, August 14:332–334, 1971.
6. Bunnell, C. B. and Monif, G. R. C.: Interstitial Pancreatitis in the Congenital Rubella Syndrome, J Pediatr 80:465, 1972.
7. Donowitz, M. and Gryboski, J. D.: Pancreatic Insufficiency and the Congenital Rubella Syndrome, J Ped 87:241–243, 1975.
8. Menser, M. A., Forrest, J. M., Honeyman, M. D., and Burgess, M. C.: (Letter) Diabetes, HL-A Antigens and Congenital Rubella, Lancet 2 (7895):1508–1509, December 21, 1974.

The Mount Sinai Journal of Medicine
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

MEDICOLEGAL NOTES

MICHAEL G. MACDONALD, J. D. and KATHRYN C. MEYER, J. D., Coeditors

Confidentiality between Patient and Doctor

The confidentiality of communications between physician and patient has long been a fundamental tenet of medical ethics. The majority of physicians take very seriously their obligation to protect patient confidences from disclosure. Nevertheless, the legal protection afforded such confidential information has always been considerably more tenuous. The physician-patient testimonial privilege, which restricts disclosure of medical information in court proceedings, is subject to multitudinous exceptions and restrictions, while the patient's right of privacy, which permits him to recover damages for unauthorized disclosures, has only been recognized in a limited number of cases.

Two very recent court decisions, one involving the United States Supreme Court and the other New York's lowest level trial court, illustrate the low priority assigned by the courts to protecting medical disclosures. The Supreme Court case, *Whalen v. Roe,* involved a challenge to New York's Controlled Substances Act of 1972. Under this law, copies of all prescriptions for certain drugs classified as dangerous (e.g., opium derivatives, cocaine, methadone, amphetamines, and methaqualone) must be forwarded by the physician to the Department of Health. The prescription form indicates the name of the physician, the dispensing pharmacy, the drug and dosage, and the name, address, and age of the patient.

Several groups representing both patients who regularly receive these drugs and physicians who prescribe them brought suit challenging the constitutionality of the Act. They argued that fear of the use the State might make of the information had interfered with the ability of patients to make decisions about their health care and that in fact in some cases patients who needed such drugs had foregone treatment. This, they argued, impermissibly interfered with the physician-patient relationship and violated both the patients' and the physicians' privacy rights. The Court, however, was unimpressed. In a unanimous decision, the Justices held that the statute was a reasonable exercise of the State's power to control drug abuse. Disclosure of private medical information was often an essential part of modern medical practice and requiring such disclosure to representatives of the State did not automatically amount to an impermissible invasion of privacy. The statute represented a reasonable attempt to regulate a public problem and contained sufficient controls against improper disclosure by the State. Finally, the

From the Legal Department, The Mount Sinai Medical Center, New York, N. Y. 10029.

Court found no evidence that patients actually had been discouraged from taking medication.*

The second case arose at the opposite end of the judicial hierarchy, the New York County Supreme Court. Beth Israel Medical Center had turned over a patient's medical record to an attorney for the purpose of collecting an unpaid bill and the patient sued claiming violation of his right of privacy. Although noting that the disclosure to the hospital attorney was proper, the court went on to declare that "mere unauthorized disclosure of patient information" did not give a patient the right to sue a hospital. In other words, when a hospital breached its duty to keep patient information confidential, there was nothing the patient could do unless he could show either an intention to harm, that the information disclosed was false, or that the disclosure was for advertising purposes.

Neither of these cases represents the last word in the area. Litigation on the subject will continue and undoubtedly in some cases courts will find that the disclosure is of such a magnitude to warrant a finding that the patient's right of privacy has been violated. Nevertheless, the two decisions indicate a lack of sensitivity to the dilemma of the patient and his physician. Proper medical care requires full communication between patient and doctor. Such communication will only occur if patients feel confident that their disclosures will go no further. Legislation requiring physicians to report confidential information, and refusals by courts to permit patients to sue for unauthorized disclosures, can only have the ultimate effect of interfering with patient care. The potential for such interference is increased dramatically by new developments in systems for retention and dissemination of information. It may be time for groups representing physicians and hospitals to join with patients' rights representatives in advocating a strong law for protecting the privacy of medical information.

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* The Court cited as evidence for this the fact that 100,000 prescriptions a month were being filled. However, there is no indication whether this is the same number as would have been expected without the statute.

The Mount Sinai Journal of Medicine
Vol. 44, No. 4, July-August, 1977
Printed in U.S.A.

ENDOSCOPIC NOTES

JEROME D. WAYE, M.D., Editor

Multiple "Spot" Biopsy Technique for Infiltrative Gastric Carcinoma

Submitted by

ALAN R. ALTMAN, M.D., STUART FINKEL, M.D., and JEROME D. WAYE, M.D.

Endoscopic biopsies of patients with infiltrative carcinoma of the linitis plastica type are often nondiagnostic. A technique has been developed of taking multiple increasingly deeper biopsies from the same target site, thereby sampling deeper into the submucosa.

Patients who present with the clinical and roentgen features of linitis plastica pose a significant diagnostic problem. Although most commonly associated with infiltrative adenocarcinoma, the x-ray findings may be simulated by syphilis, sarcoma, Hodgkin's disease, leukemia, phlegmonous gastritis or Crohn's disease (1). Diagnosis rests on multiple endoscopic biopsies and cytology, which are frequently unrewarding. In the series presented by Winawer, only two of six patients with gastric carcinoma of the linitis plastica type had positive biopsies, and both of these cases had an exophytic component. The remaining four cases with infiltrative adenocarcinoma all had negative endoscopic biopsies and cytology (2, 3). We have developed a technique of obtaining a tissue diagnosis in cases of infiltrating gastric adenocarcinoma where the standard method of multiple surface biopsies was nondiagnostic. Our method involves taking multiple progressively deeper biopsies from the same target site. A report of an illustrative case follows:

An 87-year-old woman came to The Mount Sinai Hospital with the chief complaint of several weeks of early satiety, regurgitation of solid foods, anorexia, and a 12-lb weight loss. The remainder of the history was noncontributory. Positive physical findings were confined to the abdomen where a firm, nontender, 6 cm × 4 cm mass was palpated in the right epigastrium. Initial CBC, ESR, SMA-12 were within normal limits. Upper gastrointestinal x-ray series revealed a rigid, contracted, nondistensible stomach, strongly suggestive of linitis plastica (4) (Fig. 1). Upper endoscopy was performed and revealed marked contraction and nondistensibility of the body and distal stomach with marked narrowing of the gastric lumen. The mucosa appeared dull and slightly edematous. On grasping the mucosa with biopsy forceps it

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From the Department of Medicine, Division of Gastroenterology, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Jerome D. Waye, M.D., 1065 Park Avenue, New York, N. Y. 10028.

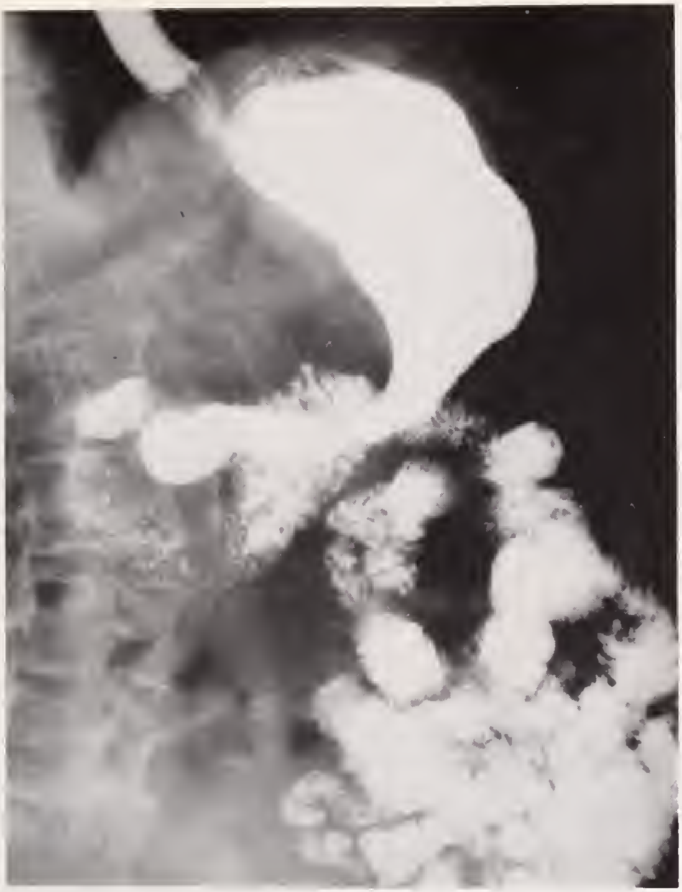

Fig. 1. Upper gastrointestinal series showing rigidity and nondistensible narrowing of stomach, typical of linitis plastica.

appeared bound down to deeper tissues. Multiple "routine" surface biopsies were taken of the obviously involved areas. Pathologic interpretation revealed only chronic inflammation, and in an attempt to prove the diagnosis, the endoscopic procedure was repeated. The initial findings were confirmed on the second endoscopy. Two sets of biopsies were taken during the second endoscopy. The first set was the standard method of multiple (six) random biopsies of grossly abnormal areas. The second set consisted of 4 sequential biopsies from the same target site with each specimen taken deeper into the gastric wall as if boring out a well. This technique is easily accomplished by fixing the endoscopic controls and maintaining constant visualization of the target area. Each set of specimens was submitted separately for histologic examination. Again, no specific pathologic diagnosis could be made from the tissue obtained by the standard multiple biopsy technique (Fig. 2), but the "well-technique" biopsy specimen revealed adenocarcinoma of the linitis plastica type, with increased stromal reaction (Fig. 3).

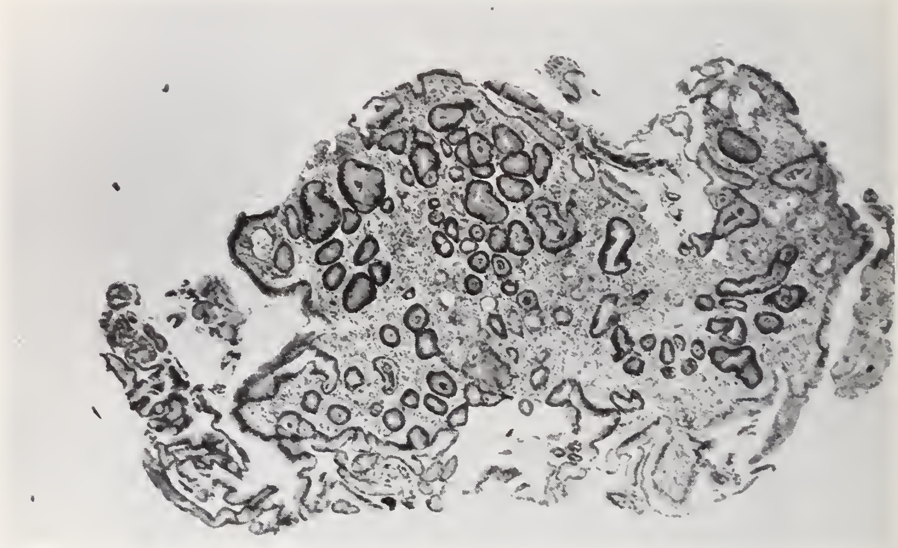

FIG. 2. Superficial biopsy, obtained by standard biopsy technique during second endoscopy; no tumor evident.

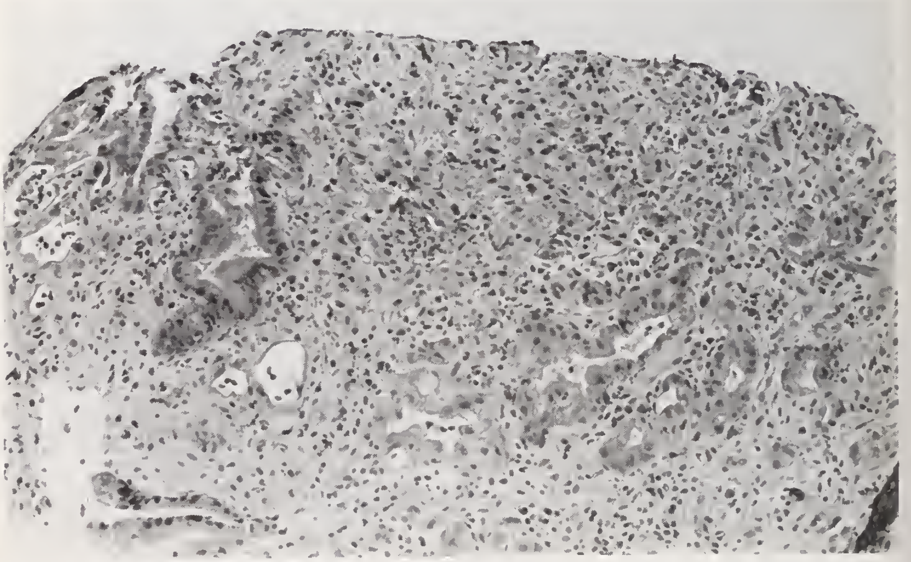

FIG. 3. One of sequential biopsies taken by "well technique"—deep biopsy rewarding in showing obvious infiltration with tumor cells as well as increase in stromal reaction of this scirrhous-type adenocarcinoma.

A technique of taking multiple increasingly deeper biopsies from one spot has evolved in the search for increased diagnostic yield in endoscopic biopsy of infiltrative, primarily submucosal gastric disease. In this presentation and in two other instances when it was attempted by one of us (JDW) it has rendered the diagnosis of infiltrative adenocarcinoma of the linitis plastica type. It seems reasonable to extend its use to all submucosal lesions, specifically to submucosal tumors and lipomas, providing that the x-ray demonstrates thickening of the gastric wall. This technique may be dangerous if the gastric wall is thin, or if the site of boring-biopsies is in the nonthickened antrum rather than over a rugal fold.

References

1. Palmer, W. L.: Carcinoma of the Stomach. *Gastroenterology* Vol. I, 3rd Edition. Edited by H. L. Bockus, W. B. Saunders Co., Phila., 1974, pp. 971–974.
2. Winawer, S. J., Posner, G., Lightdale, C. J., et al: Endoscopic Diagnosis of Advanced Gastric Cancer—Factors Influencing Yield, Gastroenterology 69:1183–1187, 1975.
3. Sherlock, P. and Winawer, S. J.: Diagnostic Techniques in Gastrointestinal Cancer, Clin Bul (MSKCC) 3:127–133, 1974.
4. Brandborg, L. L.: Polyps, Tumors and Cancer of the Stomach. *Gastrointestinal Disease*. Edited by M. H. Sleisenger and J. S. Fordtran. W. B. Saunders Co., Phila., 1973, pp. 588–590.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 4, July–August, 1977
Printed in U.S.A.

THE STUDENT'S CORNER

ALEXANDER AMBROZ, B.S., EDITOR

This column is a forum for medical students to comment on issues concerning medical school and medical education. The editor of this column is a third-year medical student and elected student representative at Mount Sinai School of Medicine of The City University of New York. Mount Sinai School of Medicine students are invited to take advantage of this opportunity to reach a wide and influential readership. Medical students from other schools are also invited to contribute.

Contact Mr. Ambroz through Mount Sinai School of Medicine, The Annenberg Building, Room 13-98A, Fifth Avenue and 100 Street, New York, N. Y. 10029. If you do not have time to write an entire column, you still can contact Mr. Ambroz and share your thoughts on a particular topic which perhaps can be incorporated into a future column.

David A. Dreiling, M.D.
Editor-in-Chief

THE ROLE OF NUTRITION IN MEDICINE

Submitted by

EDWARD CAPPARELLI, B.S.*

Nutrition is a word that has achieved a great deal of popularity in the last few years. The writings of Adelle Davis and others have made Americans nutrition-conscious. Many people still seek the "perfect" diet. Some reducing diets promise that "you can eat all you want and still lose weight." Hundreds of health food stores and restaurants continue to open, and sales of megavitamin preparations in almost every drug store are high. Everyone has something to say about nutrition and how people should eat. There are claims currently being made that link almost every disease known to medical science with a dietary deficiency of a given vitamin or mineral.

In these days of such great interest in the field of nutrition, it is amazing that physicians, those who are responsible for most of America's health care, seem to show little or no interest or concern. A recent study carried out by Dr. Esther Nelson (1) gives some insight into the reason for this general apathy. It pointed out quite clearly the paucity or total lack of nutritional training or exposure given to medical students in medical schools throughout the country. In my own first year and a half of medical school, I have noted that all the exposure to nutrition has dealt with several extremely uncommon congenital enzyme deficiencies for which limited treatment is available (e.g., phenylketonuria) and the uncommon hyperlipidemias for which nutritional intervention is helpful but was never discussed. These have been emphasized repeatedly in several courses while the more practical areas of nutrition have been avoided as if they were unimportant in the practice of medicine.

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* The author is a third-year student at Mount Sinai School of Medicine of The City University of New York. He majored in nutrition at Massachusetts Institute of Technology and has done fieldwork in Central America.

In evaluating this position, we as future physicians need to step back for a moment and objectively ask ourselves, "What role should nutrition play in medical practice today?" This is a very difficult question to answer objectively for people who have habitually thought of treatment in terms of pharmacologic and surgical interventions and have neglected nutrition as an important component. This unfortunate attitude has made it impossible for a physician competently to deal with a great many of the diseases that confront him in his daily practice. Coronary heart disease, diabetes, and hypertension all require close dietary control as a part of their proper management, but the majority of physicians are incapable of providing this service individually geared to the patients needs and food preferences so that they will comply. Although a great many Americans are overweight and all doctors know the many possible dangers associated with this condition, the best advice most doctors are able to give is, "You'd better lose some weight," without any definitive suggestions as to how this can be accomplished while maintaining a balanced diet. Even in hospitals with staff dieticians, the physician needs to understand his patients' nutritional needs and appreciate therapeutic diets and what they can and cannot do so that he can intelligently order a diet for his patients. Outside the hospital, a physician can no longer depend on a dietician, and he must be capable of providing his patients with information and dietary regimens.

Throughout life, an adequate diet is very important. Inadequate nutrition can predispose to general malaise and weakness, inability to learn or work to one's fullest capacity, and a greater susceptibility to infectious illnesses. This is especially true during periods of stress such as infancy, puberty, pregnancy, and old age, as well as during and after episodes of illness. While physicians are trained in the many other areas of history taking, very few are able to take and evaluate a dietary history. This is crucial if a physician is to identify problems and encourage beneficial dietary modifications.

Aside from the aformentioned areas of patient management, a great many patients come to their family physician with questions about nutrition and dieting. While the physician is a very competent source of accurate information on many other aspects of health and disease, when it comes to nutrition, he knows no more than the average man on the street and considerably less than some. One result is the dissemination of incorrect information and by physicians. Another is the inability to provide any information at all. Either can be potentially harmful to the patient.

As we have considered several areas of medical practice, it is quite clear that nutrition should be playing a more prominent role than it currently is. In order to accomplish this goal, more time must be devoted to nutrition during the educational process provided for medical students. As Dr. Nelson has mentioned, "From personal experience in teaching this subject (nutrition) in two medical schools, I feel that anything less than 20 hours is not meaningful in providing real ability in prescribing diets" (1). Instruction should be given in taking dietary histories and in prescription of therapeutic diets so that the physician can work better with the hospital dietician and can more adequately manage patients outside of the hospital setting. The physician should know what constitutes a balanced diet and how he can help a patient maintain one under a variety of different circumstances. Exposure should be given to the various types of diet therapy as well as the fad diets (e.g., vegetarianism, the Zen macrobiotic diet, and the megavitamin diet) – teaching what each one is composed of and what the benefits and risks of each one are. In this way, the doctor can be a more knowledgeable source of nutritional information and advice to his patients. A course in nutrition incorporated into the curriculum of medical schools could be very influential in preparing new physicians better to care for their sick patients; and, in an age of preventive medicine, these physicians will be better able to keep their patients healthy.

References

1. Nelson, E. S.: Nutrition Instruction in Medical Schools-1976, JAMA 236:2534, 1976.

Foreword

Having spent the past 35 years of my active career as a surgeon within the Mount Sinai medical complex, I was in the unique position first of Intern, then Resident, Fellow, Junior Attending, Director of Surgery at the Greenpoint and Elmhurst Affiliates, and finally Acting Chairman of the Department of Surgery, to witness the growth from a small hospital of international repute to a medical giant spawning at long last a medical school. This growth and maturation was the result of an incredibly dedicated and puissant Board of Trustees led by men of great vision and accomplishment.

This festschrift on the occasion of the 125th Anniversary of the Hospital pays tribute to two of these great leaders, Joseph Klingenstein, during whose tenure as President of the Board of Trustees the Hospital expanded to its present dimensions as a center for tertiary care, and Gustav M. Levy, a remarkable man of action who, stimulated by the vision and persuasions of Hans Popper, created the medical school.

It is proper that this issue be dedicated to the influence of the laity in Medicine, the enormous problems faced by the hospital in the delivery of medical care at the present time, as well as the challenging responsibilities confronting the medical schools in the training of physicians to deliver this care and in the maintenance of the scientific competence of the doctors following graduation.

David A. Dreiling, M.D.
Editor-in-Chief

GUSTAVE LEHMANN LEVY
1910–1976

In Memoriam

GUSTAVE LEHMANN LEVY

1910–1976

The fact of Gustave Lehmann Levy's death on November 3, 1976 continues to evoke a profound emotional response in the consciousness of all of us at Mount Sinai—Trustees, physicians, faculty and administrators, as well as employees on every level. For rarely has one man affected an institution and its constituents as did Gus Levy in his fourteen years of Mount Sinai leadership.

Mr. Levy's talent for constructive enterprise, previously proven in his successful business career, had already shown to good advantage in his volunteer activities before he joined the Board of Trustees at Mount Sinai in 1960. He had served for three terms as president of the Federation of Jewish Philanthropies before joining our Board, and was a director of the Lincoln Center for the Performing Arts and of the Greater New York Fund. He understood the myriad needs of New Yorkers and the intricate relationships among New York's many voluntary institutions.

In 1962, Mr. Levy was elected the sixteenth president of The Mount Sinai Hospital, succeeding Joseph Klingenstein, who had held the office for six previous years. With the establishment of the School of Medicine and the Medical Center in 1968, he assumed the chairmanship of the three boards.

We could use many measurements in our assessment of Gus Levy's tenure. Catalyst, organizer, and, above all, decision maker, the imprint of his leadership is seen in all of the many Mount Sinai achievements of the past 14 years. To omit the contributions of those who came before him or those of his colleagues on the boards would not present the total truth, but there are few, if any, who would gainsay the new purposiveness and momentum which began to build with his accession to office. Plans became reality, aspirations were translated into achievements.

Paramount among these achievements was the creation of the Mount Sinai School of Medicine. In the fifties proposals had been presented which recognized the national and regional need for new undergraduate medical training facilities as well as the advantages such a school would present as a reservoir of talent for the Hospital. Still, while some of the initial steps had been taken prior to 1962, everything went into high gear after that date. Typically, in 1963, Gus Levy announced to the press that Mount Sinai would accept its first students in 1968. It was the first of our stated goals under his leadership which were to be attained with timetable precision.

The Annenberg Building, which towers over the Mount Sinai complex, is a fitting symbol of the Levy years. There were many whose personal generosity surpassed the normal expectations of philanthropy, notably the Annenberg family, but it took Gus Levy's special brand of imagination and courage to accept responsibility for meeting the seemingly endless demands of the building's planners. As the blueprints continued to pile up to accommodate new facilities and expanded services, so did the budget, which was also subjected to massive inflationary pressure. In quantum jumps, construction costs went from approximately $75 million, past the $100-million mark to its final price tag in excess of $117 million.

The Annenberg Building was completed in 1974, dedicated in fine style, and immediately put to work. At its core, on the 10th and 11th floors, is the Gustave L. and Janet W. Levy Library, which has been described as a "vital educational center." It is a fitting memorial to the man who provided the vital spirit essential to such a huge undertaking. Last year the Development Committee was able to announce the completion of its $152 million capital funds campaign, thus marking the end of another era in the 124-year history of Mount Sinai.

In June 1977, at the commencement exercises of Mount Sinai School of Medicine, he was given the honorary degree of Doctor of Humane Letters. It was his third honorary doctorate; others were received from Syracuse University and Tulane.

Gustave Levy came to New York from his native New Orleans when he was 18 years old. He had spent a year at Tulane University, but his widowed mother was unable to pay his tuition. So, he came East and he took his first job as a runner for Newborg and Company, a brokerage firm. For a time he lived at the 92nd Street YMHA and in his maturer years was fond of relating that he owed the "Y" $2 when he moved. He repaid the debt handsomely, becoming a major supporter of the institution as well as its parent organization, Federation. His debt, in his words, was far greater than his $2 delinquency: "They gave me friendship and confidence in myself at a time when I needed it badly."

From these beginnings he became what the New York Times has described as "one of the most powerful men on Wall Street." After five years with Newborg, during which time he attended evening classes at New York University, he joined Goldman, Sachs, an investment banking firm with whom, except for a break for World War II service in the Army Air Force, Mr. Levy was to spend the remaining 43 years of his life. Starting at an annual salary of $1400, he grew in the company until 1969, when as senior partner he became the head of the firm. A member of the Board of Governors of the New York Stock Exchange, he served as chairman from 1967 to 1969. In addition, he was a commissioner of the Port Authority of New York and New Jersey.

A sampling of his extracurricular activities suffices to demonstrate the range of his interests in addition to his remarkable ability to hold a multiplicity of key positions simultaneously, giving each of them appropriate attention. Mr. Levy was treasurer of American Friends of Canada Committee and a member of the Board of Councilors of the Andrus Gerontology Center, University of Southern California, and the Advisory Board of The Center for Strategic and International Studies. In addition to Federation, he was for years a strong supporter of the United Jewish Appeal, and most recently served as chairman of their combined fund-raising campaign.

JOSEPH KLINGENSTEIN
1891–1976

In Memoriam

JOSEPH KLINGENSTEIN

1891–1976

A 35-year romance between Mount Sinai and a most remarkable man ended when Joseph Klingenstein died on November 11, 1976, at the age of 85. Mount Sinai old timers, physicians and others, eagerly testify that only love could have motivated the kind of deep, personal concern for patients, physicians, and personnel evinced daily by Joseph Klingenstein from his very first days as Trustee in 1941.

From one such old timer we learn that "Joe Klingenstein was always for the underdog. If you had a complaint, you let him know about it. And, if it required Board action, he saw to it that it happened."

Another frankly admiring witness tells how, as chairman of the Outpatient Care Committee, he would personally interview each physician applying for clinic duty, not for his medical credentials, but to assay the depth of the applicant's commitment to his nonpaying patients.

Those were simpler days, and today's financial crunch was certainly not their daily fare, but even in the relatively uncomplicated fifties, Mr. Klingenstein's kind of devotion and personal interest was unusual if not unique. He would make unannounced rounds of clinics and patients on any day of the week and at any time of day (he was here six days a week), not to "catch" anyone, but to be sure that our patients were receiving proper attention.

Mr. Klingenstein was described recently as "always surprising us." A diffident man, of genuine modesty, he was reluctant to be a speechmaker, a function dictated by his position. But when he did mount the platform to speak, "he was always interesting, always fresh, and, most of all, he had a delicious sense of humor."

The words modesty and dignity keep recurring like echoes when one speaks to the people who knew Mr. Klingenstein intimately. Perhaps his most significant contribution to Mount Sinai, that grew out of his interest in psychiatry, was the construction of the Klingenstein Clinical Center. It was his concept and he was particularly effective in raising funds for the building. But when it came to naming the building, it was done over his strenuous and unquestionably sincere objections.

The story of KCC's conception reveals another facet of Mr. Klingenstein's personal approach. At a meeting of physicians and Trustees, he asked, "Why aren't we building the Psychiatric Institute?" When the answer was given that we don't have money, his immediate response was, "You build and I'll worry about the money." Characteristically, he raised the necessary funds, capping the drive with a sizable contribution from himself and his wife, Esther, who shared in many of his accomplishments in Mount Sinai's behalf. At a later date, they established a chair in psychiatry. Mrs. Klingenstein died in 1974.

The word "worry" was frequently used by Mr. Klingenstein, who often referred to himself as a "worrier." Many of his colleagues report that he would call them optimists when they didn't share his somewhat gloomy view of the Hospital's state of affairs. So much so, that one member of the staff in a speech made when Mr. Klingenstein received the Jacobi Medal from the Associated Alumni in 1961 said: "He has done for the art of worrying about the hospital what IBM has done for the automatic computer: he has made it work; he has turned the art of worrying into a positive and productive force."

In that same memorable address, the speaker extolled Mr. Klingenstein as "the father of integration" in his espousal of close doctor-trustee relationships, declaring: "He is that rare hospital president who believes, and is not ashamed to say out loud, that doctors, and particularly the attending staff, are important in a hospital." It was a pleasantry, but revealing of the deep affection Mr. Klingenstein had earned in his frequent contact with so many in the Mount Sinai family.

Like other Mount Sinai Trustees who attained high offices on our Boards, Mr. Klingenstein received his basic training in philanthropy at the Federation of Jewish Philanthropies. A half-century of involvement at Federation was culminated last year when he received their Distinguished Service Award, a distinction which has been bestowed upon fewer than a half-dozen outstanding leaders in the organization's long history.

Although Mr. Klingenstein's preoccupation with Mount Sinai consumed much of his time and energy, he was a member of the executive board of the American Jewish Committee and a long-time Trustee of Temple Emanu-el.

In addition to Mr. and Mrs. Klingenstein, other members of their family shared their involvement with Mount Sinai. His brother, Percy, has had a distinguished career as a surgeon and is an Emeritus Clinical Professor in the School of Medicine. One of his two sons, Frederick, is a Trustee and a member of the Center's Campaign Steering Committee.

He is survived by another son, John, three sisters and eight granchildren, who according to all accounts were a source of great joy during his later years.

Much has been said of Joseph Klingenstein's devotion to Mount Sinai as demonstrated by his presence here six days a week during his more active years. It is worthy of mention that his closeness to the institution never lessened, so that in his last years, after having been weakened and having suffered a diminution of mobility as the result of a stroke, Joseph Klingenstein never missed an important event in the Mount Sinai calendar. His presence, even to those who did not know him as a younger and more active man, was ever an inspiration. His memory will continue to serve.

The Mount Sinai Journal of Medicine
Vol. 44, No. 5, September-October, 1977
Printed in U.S.A.

Gustave L. Levy and the Development of the Medical School

HANS POPPER, M.D., Ph.D.*

The importance of individuals in shaping historical events is argued, and the philosophy of the historian determines his emphasis either on circumstances or the individual. The influence of Gustave L. Levy on the foundation of the Mount Sinai School of Medicine is a case history illustrating the major role one person can play. Tracing this role may also contribute to the understanding of the forces that were at work in the creation of a medical school in an urban setting, based on the strength of a hospital rather than a university. The background, the motivation, the planning, the foundation, and the development of the school reflect and express this role.

The Background

The Mount Sinai Hospital was founded in 1852 (1). As did all hospitals at that time, initially it served the indigent, in this case the Jews of New York. Soon the composition of its staff was affected by transnational influences that had characterized the development of Western medical education through the years (2). Formal medical education in the West probably started in the seventh century in Salerno near Naples. Legend has it that a Salernan joined with a Greek, a Saracen, and a Jew in the foundation of the first medical school, and Arabian medicine served as a strong pillar. Several centuries later, medical schools developed in the distinguished universities of France and Italy. The influence of the other faculties—theology, philosophy, and law—explains the emphasis on the lecture as a tool of education. Leyden deserves the credit of site and Boerhaave of leadership (3) in teaching medicine at the bedside and his students transplanted the system to Edinburgh, Vienna, and Göttingen in the nineteenth century. During the French Revolution, the center of teaching was transferred to categorical departments in the large hospitals of Paris, creating the basis of clinical science (4). Until very recently, clinical observation remained the strength of French medicine, whereas in the Germanic countries the university medical school emphasized basic sciences. England balanced both forms. The distinguished hospitals served as cores of medical schools and the great universities in Oxford and Cambridge as centers for scientific progress. Scotland combined the hospital and the university.

The staff of The Mount Sinai Hospital, composed largely of immigrants or their immediate descendants, reflected a synthesis of these transcontinental movements even at a time when the thrust of progress in medicine had not yet moved from the old to the new world. Emphasis on meticulous clinical observation was combined with scientific inquiry supported by clinical laboratory investigation. It resulted in the identification of a large number of disease entities as well as in concepts of the basis of diseases during the first third of this century, well described in the anniversary issue of the *American Journal of Medicine* in 1952. Two factors contributed to these achievements. One was the close contact of members of the hospital staff with Europe, particularly Central Europe, the area of origin for so many of the physicians. This facilitated rapid application of, mainly clinical, advances made there and explains why some of the clinical laboratory departments like chemistry, hematology, and biophysics were the first in any American hospital. The second factor was the prevailing discrimination in this country that prevented graduates of other medical schools from developing in their original places of study. Mount Sinai was thus blessed with an abundance of talented and ambitious physicians. It was characterized by a fierce competition, and only the best and toughest remained on the staff. This created an institution renowned for excellent medical care and inquiry in clinical scientific problems.

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* Gustave L. Levy Distinguished Service Professor, and President Emeritus, The Mount Sinai Medical Center, and Dean Emeritus, Mount Sinai School of Medicine of The City University of New York

Requests for reprints should be sent to: Hans Popper, M.D., The Mount Sinai Hospital, Fifth Avenue and 100 Street, New York, N.Y. 10029.

After World War II, a conspicuous change took place as the momentum of medical progress moved to the United States. First, the temporary decline of Central European medicine closed the previous lifeline of information to Mount Sinai. Secondly, sciences basic to medicine, such as biology, chemistry and physics, assumed increasing importance in medical research, education and, eventually, medical care, replacing or supplementing in usefulness the clinical laboratory sciences. The location of the basic science departments on medical school or university campuses promoted a leadership of academic medical centers, where the teaching hospital is closely affilitated with a medical school and a university and is frequently located on the campus of a university. Thirdly, the discrimination gradually subsided, permitting the young doctors to get their postgraduate training and academic development in the medical schools. Thus, despite the institution of a full-time clinical staff (initially of chiefs only), the preeminence of Mount Sinai in American medicine gradually declined around the middle of this century. Nevertheless, The Mount Sinai Hospital still ranked twenty-seventh among all institutions in the country in dollar volume of research grants from the National Institutes of Health, which had become the main source of research support for the eighty medical schools and health research institutions in the United States at the time.

The Motivation

Although sentiments for developing a medical school at Mount Sinai had been expressed repeatedly through the years, several factors led to a more intense consideration of a school in the late fifties. The Bane Report, "Physicians for a Growing America," was issued in October of 1959 by the Department of Health, Education and Welfare. It stressed the need for more physicians. At the same time, many house staff members were leaving the hospital for careers in academic medical centers, depriving the institution of the previously abundant supply of young, scientifically oriented physicians. Finally, it was felt that the institution, having available both excellent medical care and well-equipped laboratory facilities staffed by both medical and biological scientists, required a new mission.

There was considerable opposition to the creation of a school inside and outside the institution. Some Trustees and staff members felt that it might be better to use available resources to further the development of the hospital rather than to devote them to the creation of a medical school that initially might be second-rate in comparison to a first-grade hospital. It was feared that a diversion of efforts, both the organizational work in establishing the school and subsequently providing undergraduate training, would produce a drain on the patient care, research and the postgraduate training for which Sinai was justly renowned. Despite the initial underestimation of the funds required, the sheer amount of money needed to found a school that would have to compete in facilities with other institutions in New York appeared as insurmountable obstacle. Moreover, organized medicine was opposed to the idea of developing a medical school on the basis of a hospital, even a strong one, because it would violate the prevalent tenet based on the Flexner Report of 1910 that only a university represents the suitable nidus for a medical school. Indeed all new schools in development at that time, stimulated by the Bane Report, were planned on campuses of universities, often with small and even distant initial clinical facilities.

Various informal contacts by members of the Mount Sinai staff and administration with the American Medical Association and the Liaison Committee on Medical Education of the American Medical Association and the Association of American Medical Colleges were in principle most discouraging. Two alternatives were therefore seriously considered. One was the creation of a graduate school at Mount Sinai, awarding advanced degrees and providing teaching laboratories. One way to achieve this would have been to strengthen the preexisting arrangement with the College of Physicians and Surgeons of Columbia University, where Sinai was recognized as a main graduate teaching facility. The other alternative was the development of the institution as a teaching hospital for undergraduate students of one of the existing medical schools, with the hope that at least some of the students would serve their clerkships at Mount Sinai. Both choices were, however, considered unsatisfactory, and in January of 1958 a group of the medical staff presented to the Board of Trustees of the Hospital, then chaired by Mr. Joseph Klingenstein, a formal proposal that Mount Sinai establish its own medical school. This was supported by a position paper outlining a philosophy. In the spring of 1958 the Board decided to establish a joint ad hoc committee of Trustees and Medical Board to study "the desirability and feasibility of either initiating our own medical school or affiliating with an existing medical school if such affiliation would give us opportunity equivalent to establishment of our own school."

The Planning

Gus Levy, who had joined the Board in April, 1960, assumed the chairmanship of this joint committee and under his dominating influence the sentiment quickly changed in favor of rapid action and progress. Negotiations were started with the City College of New York to create a medical school, but without success. In the spring of 1961, the committee had frequent meetings and a philosophy of a new school was gradually developed in animated discussion. This philosophy emphasized that Mount Sinai, which had an enviable record in patient care and medical research, would devote itself to the experiment in medical education. A new concept (5) was developed which tried to reconcile three antagonistic goals in medical education and care. The attempt was proposed to combine emphasis on quantitative biology with concern for the individual patient and his family and, thirdly, interest in the community at large. Novel curriculum ideas were developed for the planned school and indeed new terms like community medicine and core curriculum were probably used there first (6, 7). The fact that these ideas, considered visionary then, have now become cliches, attests to their soundness.

In these discussions Gus Levy and his colleagues on the Board learned the new problems of academia probably faster than the professionals. They understood that the role of a medical school would be entirely different from that of a hospital, with recruitment becoming the primary obligation of the academic staff. They realized that in the new health care and educational enterprise the young and untested school would have to be of equal if not greater importance than the old and prestigious hospital and that all professional appointments at the new combined institution would have to be approved by the authorities of the school.

When despite initial opposition the Liaison Committee was persuaded to send four representatives to Mount Sinai for an informal visit in the spring of 1961, they were impressed mostly by the sincerity of Gus and his colleagues and their report stated "if the decision to go ahead is made, the project will be pursued with such vigor, skill, and thoughtfulness that we can expect the development of a medical school with excellent academic standards." It is worth emphasizing, however, that they still expressed serious doubt about the wisdom of the enterprise.

In the meantime a report to the Mayor of New York was submitted by a committee chaired by Dr. John R. Everett, than Chancellor of The City University of New York, which emphasized that the creation of one or more new medical schools in the city would greatly benefit the city and the nation, but the committee did not recommend that the City should "assume a major part of the burden of financing a new school." However, this document, as well, pointed out the advantage of a medical school being affiliated with a university and the same opinion was stated in various contacts with officials of the American Medical Association.

The various possibiliites of such an affiliation were explored cooperatively by Trustees, administration and faculty, and Gus Levy used his excellent connections throughout the nation. By the end of 1962 an application was filed with the University of the State of New York Board of Regents for a provisional charter and the hospital appropriated an initial contribution to the School of Medicine as financial basis. In the meantime, Gus Levy had become President of the Board of Trustees of the Hospital (replacing Mr. Klingenstein, who became Chairman). In this role and as leader of the combined Trustee/faculty group, he appointed an advisory committee, consisting of distinguished scientists and medical educators, to assist in formulating the program of the school. Their appointment was probably one of the most crucial steps in the creation of the school and their names attested to the desire to obtain the best advice possible: Drs. William B. Castle, Bernard D. Davis and Robert J. Glaser of Harvard; Alvin C. Eurich, Fund for the Advancement of Education; Dr. Seymour S. Kety, National Institute of Mental Health; Dr. Vernon W. Lippard, Yale; Dr. Willard C. Rappleye, Josiah Macy, Jr. Foundation, and formerly of Columbia; Dr. Paul Weiss, Rockefeller Institute; Dr. W. Barry Wood, Johns Hopkins; and Drs. George Baehr and Paul Klemperer of Mount Sinai. The advisors met in March of 1963 and again in September with the combined Trustee/faculty committee, and under Gus Levy's chairmanship, the initial principles of the school were hammered out. Now, gradually a philosophy of the school, emphasizing a combination of biologic, physical, humanistic, and sociologic goals, developed. Serious work by all concerned began.

The Foundation

When in July 1963, the charter was granted, Gus Levy assumed the position of Chairman of the Boards of the Hospital and School of Medicine, while Milton Steinbach served as President of the School. Gus Levy announced publicly that the medical school would accept its first students in the fall of 1968—a bold step that turned out to be right. He stated "We intend to make the preclinical, or first two, years distinctive and invaluable by giving exceptional emphasis to the humanities. History, sociology, philosophy, and anthropology will be as much part of the early curriculum as anatomy, physiology and the other usual preclinical subjects, because we want to help prepare the physician to be able to relate health and disease to the society in which he functions. We will also teach computer applications, electronics, and physics, because medical research and practice are relying on them more and more." This statement illustrates how well he had mastered his new role in academia and it bespeaks the capacity of a man who previously had concerned himself primarily (and most successfully) with other civic and business activities. Many often difficult and painful decisions had to be made about financial, organizational, and architectural problems as well as regarding the selection and recruitment of administrative and professional staff. Gus made these decisions rapidly, competently, and courageously, saving years in the development of the school.

Different activities were carried out simultaneously. A master plan had to be developed coordinating organization, governance, building plans, philosophy and financial resources of the school. The help of many consultants—architects, medical and hospital planners, and management experts—had to be obtained and acting chairmen of the key departments were appointed.

The question of a university affiliation had to be resolved and many schemes were considered. These included the idea of a graduate university in which The Mount Sinai Medical Center would train other health professionals together with medical students as an "MIT of Health." The question of a Graduate School of Biological Sciences and of Human Studies associated with an Institute for Environmental Medicine was raised. Indeed even the question of creating an undergraduate college affiliated with Mount Sinai was briefly explored. Nevertheless, an affiliation with an existing university in the form of a "symbiosis" appeared the most reasonable solution. This materialized eventually in July 1967, after the appointment of the permanent Dean, in the present satisfactory affiliation, with Mount Sinai serving as a financially independent medical school of The City University of New York.

The second major task was the actual architectural planning, culminating in the erection of the Annenberg Building, which was integrated with many improvements in the rest of the physical plant of The Mount Sinai Hospital. A series of possibilities was seriously considered on the basis of detailed plans of the architects. Gus Levy and the members of the Board, particularly those with specialized architectural knowledge, were constantly consulted and their contributions and imaginative thinking made a great impact in the final results. An outstanding example was the decision, virtually made by Gus Levy alone, to have the Ambulatory Care Clinics become part of the new Annenberg structure. It reflected an understanding of the increasing importance of outpatient care in medical education and treatment at a time when its importance as a part of hospital medicine was not fully recognized.

Another bold step taken under Gus Levy's leadership was the creation of teaching and laboratory facilities in what is now the Nathan Cummings Basic Sciences Building. When it became clear that the Annenberg Building (the main site of the medical school) could not be ready to accommodate students in 1968, the date given in the first announcement, the decision was made to use the institution's own funds to acquire a bus garage near Mount Sinai and to reconstruct it rapidly into a building which would provide a site to teach a smaller group of first- and second-year students in multidisciplinary laboratories and also for the basic science departments and for the new Graduate School for Biological Sciences, another unit of The City University. Indeed in the fall of 1968 a first- and a third-year medical school class entered the new school.

A major problem was the recruitment of a permanent Dean. Gus Levy chaired the Search Committee. The selection of the Dean entailed as much discussion about the philosophic basis of the new school as about the personal attributes of the candidates. Finally, Dr. George James, the effective Health Commissioner of the City of New York, was chosen. This indicated an emphasis on an aspect of the school which was not part of the sentiment then prevailing at Mount Sinai and indeed did not elicit much enthusiasm among some members of the advisory committee. Dr. James brought to Sinai the primary concern for the community, although he did not neglect academic aspects and hospital medical care. Lasting consequences of his selection and tenure are the blooming Department of Community Medicine and the Laboratory for Environmental Sciences, two jewels in the crown of Mount Sinai set upon an institution whose staff until then had not yet been deeply concerned with these problems. Subsequent trends in American medicine have indeed justified this foresight of almost 15 years ago. In a similar vein, again at the instigation of Gus Levy, the recruitment of Dr. Solomon Berson as Chief of Medicine was a signal to the medical community that Sinai now was giving equal emphasis to quantitative biology as to excellence in clinical diagnosis.

The most important and difficult problem of the founding of the school was the almost impossible task of providing the immense funds required. It is worth remembering that in those years it was an accepted doctrine that outstanding scientists could be attracted only to a medical school that provided adequate facilities for research. In the middle sixties this meant the building of expensive large new laboratory facilities to match those of the major medical schools in the country. The Annenberg Building is probably the last large new medical school building in this country where this expensive principle has been carried out and even found support by the Federal and State governments. The almost unbelievable achievement of creating, along with the medical school, the facilities of what could be called a large new research institute requires no further belaboring.

A short chronology of the crucial events should list that the Liaison Committee could be persuaded to arrange a formal site visit to the institution. In January, 1965, a four-man team visited Mount Sinai to evaluate its basis of a new medical school. Its positive report emphasized as pillars of strength the Trustees, led by Gus Levy, and the high quality of the voluntary staff. Thus the Liaison Committee voted to report to the U.S. Commissioner of Education that "there is reasonable assurance that the Mount Sinai College of Medicine after completion of the facilities and at or prior to the time of graduation of the first class to use the facilities will have met requirements of the accreditation standards of the Liaison Committee on Medical Education." This was a prerequisite for application for funds from the U.S. Public Health Service and the National Institutes of Health. The Trustees, administration, and faculty prepared a comprehensive application for almost $26,000,000 for teaching, research, and hospital facilities. Up to that time this amount was not only the most voluminous application submitted but also the greatest amount of money requested by any school.

Another milestone was a site visit by a large committee consisting of deans, scientists, and administrators of the Public Health Service who had to be convinced that Mount Sinai deserved the funds. Gus Levy again rose to the occasion in discussions with this group. The application was approved in principle several months later, but was funded only after execution of the affiliation with The City University of New York. The appointments of faculty at both Mount Sinai and the affiliated hospitals were then completed and at the first Faculty Assembly in Sepember, 1967, Gus Levy stated: "I want you to know that you have the backing—the complete backing— of the lay Boards of Trustees of the hospital and the medical school . . . It has been long, hard work to achieve this medical school. We all know you are going to dedicate your lives to the fulfillment of this great project."

Development of the School

With the foundation accomplished, many new tasks arose. A curriculum was developed, student applicants were screened and admitted. Their number increased from year to year until eventually one hundred first-year students and more in the third and fourth year were admitted. A basic sciences faculty was recruited and the clinical faculty was enlarged to meet new educational demands. The Annenberg Building was finally completed and opened its doors. The formal dedication ceremony took place on May 26, 1974, under Gus Levy's chairmanship with the then Vice-President Gerald Ford as the key speaker and with many distinguished scientists and citizens, and the members of the Annenberg family in the audience. Gus maintained the effective leadership of what was now a well-functioning enterprise, but one that still required many bold decisions. He chaired many committees and particularly that which recruited as Dean and President Thomas C. Chalmers, who gave up the prestigious position of Associate Director for Clinical Care of the National Institutes of Health and Director of its Clinical Center. Gus Levy led the graduations, the first in June, 1970, and the other academic ceremonies of a viable school with his characteristic mixture of human and pragmatic concern. New programs, particularly in allied health education and investigation of health care delivery, were carried out, to a great degree in cooperation with units of The City University of New York. Mount Sinai became a prototype of a new medical school that influenced nationwide trends in medical education (8), and Gus Levy eventually became the Chairman of the influential Lay Advisory Committee of the Association of American Medical Colleges.

Outlook

A dream became reality by overcoming apparently insurmountable financial and intellectual obstacles. Although not all ambitious goals laid down during the planning of the school, particularly in education, were realized, partly because of the changing climate in the nation, they were the basis of The Mount Sinai Medical Center, and Gustave Levy, the leader, was not only a friend to many of us but also a key person in making the principal plans come true.

References

1. Hersh, J. and Doherty, B.: *The Mount Sinai Hospital, New York. 1852-1952*. Random House, New York 1952.
2. Snapper, I.: *Meditations on Medicine and Medical Education—Past and Present*. Grune & Stratton, New York 1956.

3. Bowens, J. Z. (editor): *Medical Schools for the Modern World*. Johns Hopkins Press, Baltimore, 1970.
4. Foucault, M.: *The Birth of the Clinic—An Archaeology of Medical Perception*. Pantheon, New York 1973.
5. Popper, H.: The Mount Sinai Concept, Clin Res 13:500–504, 1965
6. Popper, H.: New Objectives in Medical Education, Ann N Y Acad Sci 128:473–479, 1965.
7. Popper, H.: A New Curriculum, Ann NY Acad Sci 128:552–560, 1965.
8. Popper, H. (editor): *Trends in New Medical Schools*. Grune & Stratton, New York 1967.

The Mount Sinai Journal of Medicine
Vol. 44, No. 5, September-October, 1977
Printed in U.S.A.

Joseph Klingenstein and the Growth of The Mount Sinai Hospital

MARTIN R. STEINBERG, M.D.

Anyone not fortunate enough to know Joseph Klingenstein personally would quite naturally dwell on the wealth and financial benefactions in describing Joe Klingenstein's role in the growth of The Mount Sinai Hospital. We who are in the family, so to speak, realize that a true assessment must go considerably beyond the magnificient gifts of money he gave so generously. He was indeed a very wealthy man. Fortunately he was an unusual and special type of man whose unusual and special qualities extended his role far beyond that of philanthropy. Joseph Klingenstein had great dignity. Dignity is often associated with stuffiness, but he was the very antithesis of stuffy. The security that is associated with great qualities made it unnecessary for him to impose his sense of dignity on those he knew and dealt with. As a matter of fact, I am sure he himself was quite unaware that he possessed this unusual quality. He did, however, grant dignity to others. In all the many years we worked with him, we never were aware of a single instance when he said or did anything to assault the dignity of his fellow man, regardless of the man's station. He was as polite and thoughtful in dealing with the lowest echelon of employees, as he was with his colleagues on the Board of Trustees.

Joseph Klingenstein had so many strengths that he used freely on behalf of the Hospital that we shall have to confine ourselves, because of the necessary limitation of space, to just a few of the most important ones. He felt that the Hospital must be prepared to serve the widest spectrum of health demands of the community and he was as concerned that the services be comprehensive as he was that they be of the highest quality. He knew that the quality of services rendered depended a great deal on the qualities of the medical staff and their nonmedical as well as their medical assistants. Each vote, action, and gift bespoke these concerns.

He knew that the human and humane qualities of the staff and their consideration for the feelings of the patients were as important as their skills. For years he took time out of his very busy schedule to see and chat with every new physician before his appointment to the outpatient staff. Many of these physicians later spoke of these meetings with some wonder and appreciation. They expected to hear lists of "do's and don't's" and a reminder of their new responsibilities. What they got was a friendly, informal chat that encouraged them to be humane, thoughtful physicians, to be progressive, and always to keep in mind that the Hospital would remain a valuable community resource to the extent that it served its patients well.

Joe Klingenstein rarely missed a meeting of the Board of Trustees or its Executive Committee, the Outpatient Committee (which he chaired), the Committee on Psychiatry, and many others. While he spoke little, he listened a lot. When he did speak, we listened because we knew that what he said would be pertinent and helpful.

He was a modest man, self-deprecatory and always admiring of the qualities of his associates. His modesty was intense. Yet when he failed to comment on the gloomy potential of the project under discussion, we knew that we had his positive and deliberate approval and the kind of support which would ordinarily follow a more outspoken enthusiasm.

To dwell on his integrity would necessarily involve the language of the cliche. On a scale of one to one hundred there could be no doubt of his position; it was one hundred plus. When Joseph Klingenstein promised anything, whether it be money or action, it was done. He was always and absolutely responsible. When any task needed to be done or any action taken for the benefit of the Hospital, he saw to it that the assignment was accepted and if it was not, he undertook to do it himself. He never dwelled on the difficulty of a task or measured the prestige it might bring. It was necessary, so he did it.

The gift of the Esther and Joseph Klingenstein Center, and the way it was given, tells one a great deal about Joe Klingenstein. The Hospital until the early 1950's lacked two major elements of service – Obstetrics and Psychiatry. In general hospitals throughout the community the latter was either nonexistent or nominal. Psychiatric consultations were normally handled by a member of the Neuropsychiatry service, if that service had a fully qualified psychiatrist. There were few staff psychiatrists. Mount Sinai, for instance, gave necessary psychiatric service through one psychiatrist on the Neurology Service. Not a single general hospital in the entire country furnished a separate area for psychiatric beds, staff, and patients. Cognizant of this deficiency, the Board decided to study it in committee. Fortunately, Mr. Klingenstein was asked to chair the Committee on Psychiatry. With his customary thoroughness, he called a number of meetings in order to give his associates and himself the opportunity to listen to many prominent psychiatrists. In addition to these sessions in the Hospital, he spent several days visiting special psychiatric facilities in other cities and stimulated the entire committee to visit several such facilities in the City and two outside the New York area. After eighteen months of intensive study, a report was prepared that in essence called for the appointment of a full-time psychiatrist and the assignment to him of a staff which he would organize in a special area containing patient and adjunctive facilities. The report also recommended that a separate psychiatric pavilion be constructed as soon as possible. The report was so comprehensive and detailed that it was published in order to fill the many requests by other institutions. The Board of Trustees approved the report and its recommendations. In a relatively short time they were fortunate to obtain on a full time service a brilliant psychiatrist, Dr. M. Ralph Kaufman, who came from Boston to establish a full psychiatry service, the first in any general hospital in the country. A floor of the Medical Pavilion was altered to furnish patient beds and headquarters for Dr. Kaufman and several assistants and secretaries.

One might rightly expect that the Board would now look upon what had been accomplished and, figuratively, sit back and rest. That was, however, in Mr. Klingenstein's way of thinking, a job only partly completed. He called for the full completion, that is, the erection of a psychiatric pavilion. Such a pavilion was a formidable project calling for the relocation of many tenants, the demolition of several apartment houses, and the expenditure of many millions of dollars. To Mr. Klingenstein "formidable" was not a "scare word." A promise made meant a promise kept. Offering to give a substantial sum and to attract more, he got the Board of Trustees to approve the erection of a pavilion which would house not only all that was necessary for the care of adult and child inpatients and outpatients in psychiatry, but in addition, several floors for the care of medical and surgical patients.

It was characteristic of Joe Klingenstein that after all his work and his magnificient gift, without which we would not have been able to entertain the building, he did not want it to bear his and his wife's name. "Perhaps," he said "we can attract a large gift from a donor by offering to name the building in honor of himself and his family." It was only when he became convinced that it would be unfair to his wife and sons to name the building for anyone else that he finally agreed to call the Pavilion The Esther and Joseph Klingenstein Clinical Center.

I have alluded to his innate modesty. There came a time when it was necessary to replace an outgoing President. Strategically we needed a man who was well known and highly respected by the community, who was himself generous and could inspire others to help financially, a man who would generate the esteem, friendship and respect of the entire Board. In summary, we needed Joseph Klingenstein. If one searched for a position that would repel and discomfit him, one could hardly choose better than President of the Board. At first he rejected the post, and only when he was convinced that it was a necessity for the Hospital did he do what he usually did when there was a difficult job to be done, he consented.

He never relished the job but he did it and as usual he gave it his all. His unusual modesty made the necessity to speak from the podium a far from welcome chore. Yet when it was necessary, he spoke surprisingly well and displayed a captivating sense of humor. He would underplay the strategic clause and, as the meaning became clear, the audience who had come close to missing the point, now greeted it delightedly.

His stature and esteem among the Board, as well as the community at large, made it unnecessary for him to urge a difficult assignment on a colleague: "How can you say 'No' to Joe who never has ducked a tough job—not even once!" He knew how to delegate and to whom and when he did delegate he gave the man he chose complete confidence and full support.

He was cautious but reasonable and capable of changing courses when the occasion warranted such a change. He listened and became convinced that since population was growing, the demand for service would too, but that the necessary land and space to make possible increased services was static. He launched a program of housing and land expansion. Even when the Board flinched at the need to buy yet another building or piece of ground and asked

"What will we need it for?" he would answer quietly "I don't know what we need it for, but I'm sure we'll need it." The Board, knowing he never moved merely by emotion or by a blind course set in the past, would approve. As a result, we are fortunate to have secured an adequate amount of land surrounding the hospital to permit a certain latitude in planning for the future.

Joe Klingenstein never publicized his activities on behalf of the hospital. He once drew me aside and asked me to spend a day or two of my vacation visiting with an elderly friend of his who was wintering at Key Biscayne. We later received a multimillion-dollar gift from the man, not because of my visit but "in honor of Esther and Joseph Klingenstein." Let this anecdote stand for the dozens of other times he made similar efforts.

Mr. Klingenstein was not enthusiastic about several of our major projects, but he never stood in the way of decisions made by the Board or its Executive Committee. He was concerned by the great expense of the Annenberg Building but he contributed generously when the Board finally approved it. He saw it as headquarters for the medical school and he played a major role in recruiting Gustave Levy to succeed him as Chairman of the Board.

His modesty amounted almost to shyness and his reluctance to make speeches led those who did not know him well often to interpret his silence as opposition when more often than not he was in full agreement and proved it by his vote and a financial contribution.

The role of Joseph Klingenstein in the growth of the Hospital is readily defined:

Without his devotion to quality;
Without his worship of human dignity;
Without his progressive advocacy of the acquisition of land and buildings;
Without the attraction of his integrity and the unusual respect of the community, which reflected on the Hospital, and without his generous financial support . . .
The Mount Sinai Medical Center would now be years behind its present level of progress and growth.

Klingenstein and Levy: Exemplars of Voluntarism

ALFRED R. STERN

One hundred and twenty-five years ago, the Jews' Hospital in New York was incorporated for "benevolent, charitable and scientific purposes." Its founders were nine philanthropists and its initial support came from the proceeds of a charitable ball.

From its very inception, The Mount Sinai Hospital was founded on the bedrock of philanthropic giving. The name was changed from Jews' Hospital to The Mount Sinai Hospital in 1866 to reflect its service to the sick, regardless of religion or race.

The intrinsic tradition of charitable and benevolent giving to advance its scientific purposes has been continued through the past century and a quarter through the generous contributions of Trustees, physicians, grateful patients, and other members of the Mount Sinai "family." Our Trustees, in particular, have played a pivotal role in the support of our institution. When new buildings, new facilities or new programs were needed to keep Mount Sinai in the forefront of community service and medical advance, they instinctively responded by matching their own personal resources with their commitment as Trustees. This was reaffirmed during the past decade when they provided the resources, leadership, and stimulus for a new School of Medicine, the construction of the Annenberg Building, and the modernization of a number of facilities, some dating back to the turn of the century.

In so doing, they were acting in that spirit of voluntarism that has made the American health care system the best in the world. Webster defines voluntarism as "the principle or system of doing something by or relying on voluntary action." Hospitals created and nurtured by this voluntary action have assumed a position of primary importance in providing health care to Americans. Expenditures for health care represented 8.3 percent of the Gross National Product last year, and America's hospitals have become a 40 billion dollar business, among the largest of the nation's industries.

In this study for the Josiah Macy Foundation, Dr. Russell A. Nelson points out that "most of the large teaching hospitals are private, voluntary, nonprofit institutions founded in the charitable tradition of the great European asylums for the sick poor. They were built and supported over most of their history by philanthropic funds; their governance traditionally has been in the hands of public-spirited men and women, the leading citizens of their communities, who have contributed their time and talents without reward other than the inner satisfaction that comes from doing useful work for the benefit of the whole society. These institutions have been the pacesetters. It is these institutions, these leaders that must provide the initiative and take the leading role in uniting these fragmented elements of the health service into larger, more effective organizations and systems without sacrificing the vitality that is rooted in pluralism and free enterprise. The opportunity, the challenge, the responsibility are theirs."

Against this backdrop, the rare leadership qualities and contributions of Joseph Klingenstein and Gustave Levy assume sharpened focus.

Klingenstein

When the President of Mount Sinai, George B. Bernheim, asked Mr. Klingenstein to become a member of the Board in 1941, he readily agreed. He regarded Mount Sinai as "one of the foremost medical institutions in the nation. To be connected with it as a member of the Board was a high honor indeed." He took very seriously his responsibility as a member of the Board; Vice President from 1944 to 1956; its fifteenth President from 1956 to 1962; Chairman of the Board from 1962 to 1969, and Chairman Emeritus from May 1969 to his death on November 11, 1976.

Central to his service as a Mount Sinai Trustee was his concern for the patient. In his 1960 Annual Report, he defined his credo: " . . . the determined effort to have every patient, whether in private, semi-private, ward or clinic, think of Mount Sinai as a Hospital where every element of care is of the highest quality and rendered in the warmest and friendliest atmosphere."

This determination was reflected in his personal interest and devotion. Mr. Klingenstein would make unannounced rounds of clinics and patients on any day of the week or at any time of the day (he was at Mount Sinai five days a week and every Saturday morning). Serving, as many Mount Sinai Trustees have done, on search and other important functional committees, he would interview each physician applying for clinic duty, not for his medical credentials solely, but to assay the depth of the applicant's commitment to his nonpaying patients.

When he was awarded the Jacobi Medallion by Mount Sinai's Associated Alumni in 1961, a speaker extolled him as "the father of integration" for espousing [a] closer relationship between physician and Trustee. "He is that rare hospital president," the presenter declared, "who believes, and is not ashamed to say out loud, that doctors, and particularly the attending staff, are important in a hospital."

His responsiveness to Mount Sinai's needs was legendary. The story is told of a meeting of Mount Sinai physicians and Trustees at which he inquired, "Why aren't we building the Psychiatric Institute we promised Mo Kaufman and his psychiatric colleagues?" The quick response was, "We don't have the money." To which Mr. Klingenstein retorted, "You build and I'll worry about the money." In characteristic fashion, he determinedly raised the money to build the Clinical Center (subsequently named for him despite his protestations.)

Whatever philanthropic or communal seeds were latent in Joe Klingenstein, they seemed to come to flower with his Mount Sinai association. His brother, Percy, a noted Mount Sinai surgeon, observed that "Joe's high sense of civic and communal responsibility stems from his own strong obligatory feeling of commitment and duty when he became President of Mount Sinai." In naming him Honorary Doctor of Humane Letters in June 1975, he was cited for his "dignity, modesty and kindliness" and his 35 years of dedicated and compassionate service to Mount Sinai.

Levy

Gustave Levy, bold, daring, with an unerring instinct for moving forward, brought his own distinctive qualities of vision, courage, and single-minded effectiveness to his fourteen-year stewardship of Mount Sinai. Joining the Board in 1960, and elected sixteenth President of the Hospital in 1962, succeeding Joe Klingenstein, he added a new sense of purpose and momentum. Plans became reality, aspirations were translated into achievements.

Galvanizing the efforts of his fellow Trustees, building upon what had been discussed before, his paramount achievement was establishment of the School of Medicine. In the 1950's, many at Mount Sinai recognized the national and regional need for a new medical training facility, as well as the advantage such a school would present as a reservoir of talent for the Hospital. Although some initial steps had been taken prior to 1962, everything shifted into high gear with Gus Levy's ascent to the presidency. Typically, he announced to the press in 1963 that Mount Sinai School of Medicine would accept its first students in 1968. This was just one of our stated goals under his leadership that would be attained with timetable precision.

It was under his aegis that the Hospital and School of Medicine were conjoined to form The Mount Sinai Medical Center in 1968.

The Annenberg Building is an apt symbol of the Levy years. The home of the School of Medicine and many new Hospital facilities, the building was made possible by the extraordinary generosity of the Annenberg family, our Trustees, and more than 200 contributors in the $100,000-and-over category, many of whom responded to Gus Levy's compelling appeal for support. It also took his special brand of imagination and courage to accept the responsibility for meeting the seemingly endless demands of the building's planners. As the blueprints continued to pile up to accommodate new facilities and expanded services, so did the budget, which was also subjected to massive inflationary pressure. In quantum jumps, construction costs went from approximately $75-million, past the $100-million mark, to its final price tag in excess of $117-million.

But thanks to Gus's constant involvement and leadership, the Annenberg Building was completed in 1974 and immediately put to work. Most appropriately, one of the most beautiful and functional areas of the entire building is the Gustave L. and Janet W. Levy Library on the tenth and eleventh floors, the educational hub of the Mount Sinai complex and a fitting memorial to the man and his wife who provided the vital spirit essential to an undertaking of such great magnitude.

At the Seventh Commencement of the School in June 1976, Gus Levy was awarded the Honorary Doctor of Humane Letters degree. The citation stated that "Armed with conceptual powers that challenge the infinite, yet ever mindful of the next practical step, he is a rare human being. He has coupled these attributes with boundless energy to build a singularly successful role in the realm of finance while providing invaluable leadership in a formidable range of charitable enterprises. The conception, birth and rapid growth of Mount Sinai School of Medicine have been due in greatest measure to his leadership as Chairman of the Boards of the Mount Sinai institutions."

Joe Klingenstein and Gus Levy shared a mutual concern for the individual patient and love for Mount Sinai. They were also broadly involved in the community through their tireless commitment to the Federation of Jewish Philanthropies of New York. For 50 years, Joe Klingenstein was involved in the highest councils of Federation as a Trustee and a member of the Executive Committee. In recognition of this service, he was awarded their Distinguished Service Award last year, a distinction bestowed upon fewer than half-a-dozen outstanding leaders in the organization's 60-year history. Gus served for three terms as President of Federation before joining our Board and was one of its most influential leaders. Together, they epitomize the very spirit of voluntarism.

Emerson once observed that "If a man plant himself indomitably upon his instincts and there abide, the huge world will come round to him." Joe Klingenstein and Gus Levy—each in his own particular way—planted themselves upon their own instinct for the right and necessary and humanly helpful; Mount Sinai and the world are better for their having been with us.

The Mount Sinai Journal of Medicine
Vol. 44, No. 5, September-October, 1977
Printed in U.S.A.

The Current Challenge to Medical Education in the United States

REBA KASTEN NOSOFF and HANS POPPER, M.D., Ph.D.

Although the ultimate goal of every medical school is to promote health, the primary purpose is to train physicians (1). Today's health care system finds itself in crisis because of the dissatisfaction of society in general and the medical community in particular.

The available health care does not satisfy the great expectations of a society which has become increasingly sophisticated in medical knowledge and aware that available knowledge in diagnosis and management has not been made adequately available to all members of the society.

Although tremendous progress has been made in the last decades through medical research in acute diseases, particularly in wiping out infectious diseases and in handling trauma, much less has been accomplished in the pathogenesis or effective treatment of the chronic degenerative diseases, such as cancer and arteriosclerosis.

Physicians and health care facilities are inadequately distributed throughout almost every nation. Physicians are particularly concentrated in population centers in which the affluent clusters can be found. While the hospitals do not equally cover the demands reflected in patients and density of population, recent studies by Fuchs have shown that focal accumulation of physicians does not necessarily result in better care and, if anything, increases rather than reduces the expense of total care and of the individual physician's service (2).

Demands on the Medical School

The medical school plays an important role in the demand for a more effective pattern of health care by coordination in the planning strategy. It influences the health care system by training persons acting in the system, by conducting biomedical research, and by developing alternate methods of providing health care. Particularly in the last endeavor, service function in treatment of patients is implied. In this respect, the medical school plays a peculiar and in many ways specific role in the university at large. Agricultural schools of the university have been confronted by this problem even before the medical schools, and are looked upon as a test for the dilemma arising from the demands for service function (3). The agricultural school is developing and teaching methods of agricultural procedures and requires farms to carry them out; but it takes no responsibility for the conduct of farming at large. The governmental supervisors and the county agents are not under the school's control. To draw this line is difficult in the medical school where human welfare and life are at stake, not agriculture.

Another predicament lies in the necessity to predict the future health care system if one is to train health personnel to work in the system. Such a prediction is hazardous because it is based not only on the future achievements of biomedical research, reflecting a "hard" science, but also on the result of shaping a health care system by so-called "soft" sociologic sciences. However, a further difficulty is that principles of education reflecting today's morality and conscience represent the "softest" of all sciences. It has been stated (1) that in physics one cannot argue, in biology one may argue, but in education, one has to argue.

History of Abrupt Changes in Medical Education

In a rapidly changing world order, the microcosm of health care, education and research is changing less rapidly in execution than in philosophy. Predictions of the future are not only a challenging intellectual exercise, but, more important, a guideline for action.

If one has to decide on an experiment in medical education based on predictions of the future and on feelings, but hardly facts in education, one might benefit by reviewing briefly the history of medical education, particularly in the United States, where the development was compressed into hardly more than 200 years. In this period several abrupt changes developed which might be dignified by the term revolution. Moreover changes occurred both in hospital development and in biology which encourage us to correlate the development in medical education with those in hospitalization and biology.

In the colonial period of America, medical schools were already founded in close affiliation with universities. For instance, the School of Medicine of the University of Pennsylvania was founded in 1765 as Medical Faculty of the College of Philadelphia, and the Medical School of Columbia University, created in 1768, later to become the College of Physicians and Surgeons, dates back to the King's College founded in 1754. The university as a community of scholars encompassing all the various aspects of human endeavor appeared a most desirable site for medical education as it has been in Europe for generations. But on the North American continent, physicians were trained mainly as apprentices of their elders rather than in schools, and an academic revolution in the latter part of the previous century was required gradually to enforce medical education in schools. However, this led to a greater concentration of physicians in hospitals, and this in turn started to reduce the house call in favor of the hospital visit. Originally, hospitals were only places for the indigent sick, which means they served primarily as almshouses, as shelters, as nursing homes. Biology in this early time was primarily descriptive or taxonomic.

Around the turn of the century another abrupt change occurred in medical education when around 1900 the Johns Hopkins Medical School first came into being, conscientiously adopting the principles which had brought German medical schools, under university sponsorship, to their peaks of achievements. Abraham Flexner presented his famous report in 1910, commissioned by the Carnegie Foundation (4), and started a revolution by making biology the cornerstone of medical education. Pharmacology, for instance, concerning itself with the drug action in the body, replaced materia medica dealing with description of therapeutic agents and empiric presentation of the subjective changes produced by them.

The Flexnerian model of medical education produced great achievements in American medicine, achievements for which the nation was envied by the entire world, but a price was exacted. The product of medical education was standardized by lockstep training equal all over the country where creditation procedures weeded out inadequate schools and maintained a uniform product in the surviving ones. Moreover, the emphasis on the biologic processes resulted in some alienation of the physician from the patient, luring him away from the bedside.

Meanwhile, the hospitals underwent rapid changes. Now the affluent stratum of society also sought help in the hospital where highly equipped laboratories, some in close correlation with the bedside, had sprung up endowed with sophisticated equipment. The hospitals provided the concentration of medical know-how and manpower. In the early part of this period biology emphasized understanding of development; but around the middle of the century, molecular biology developed as the queen science—as a triumph of correct thinking.

Somehow around the middle of the sixties, despite continued success, the climate changed not only in society at large but also in the schools. With the young students and faculty in the forefront, a sociologic revolution in medical education developed which called excellence elitism. It emphasized personal dignity and claimed that the biologic approach does not do full justice to the feelings and mind of each individual. Sciences previously in the background of medical thinking became suddenly important—psychology, sociology, anthropology, economy and philosophy, and ethics. Since these disciplines always had their home at the university campuses, the affiliation with the university acquired new meaning, and mutual exchange between the medical school and the other faculties became more important. At the same time, interest in the patient in the community arose, and the medical school extended its reach far beyond its original borders, thus widening radically the scope and also the obligations of the medical school. Simultaneously, within the hospital, the outpatient department acquired more importance both in teaching and research, and much of the interest of the school started to center upon the community health centers as "new laboratories" of the medical school.

The situation was complicated by the technical development of medical specialization which created a scarcity of primary physicians. House calls virtually disappeared in cities, urban and farm areas. "Maldistribution" of doctors became a slogan. This sociologic change influenced medical teaching with the following emphasis:

1. Earlier contact of students with patients as early as the first year of medical studies.
2. Extended teaching of social sciences.

3. Introducing the student to the realities of today's medical needs because about 90 percent of all medical care takes place neither in the hospital bed nor in the doctor's office.

4. Early emphasis on psychiatry and behavioral research. This led on the one hand to closer contact with nonmedical faculties, but on the other hand to a relocation of teaching and health care from medical centers to community health centers where nonmedical health care workers play an important role.

Meanwhile, environmental biology, playing a greater role with the suspicion that 80 percent of all cancer is caused by environmental factors, began to challenge the "queen science"—molecular biology.

Types of Physicians in Future Health Care System

This sociologic revolution raised some questions. Where do we go from here? What type of physician and health worker should the school train? What type of health care do we want? Research in biological sciences remained the only stable area because the medical profession, through its schools, knew exactly what it wanted to achieve. Even in these areas questions as to the social value of biologic research have recently arisen with the serious belief that the priority of studies in biologic research should be determined by social considerations.

The medical school then is involved on several levels with the quality of the physician:

1. It selects the student to become a physician by the admission process. Much disagreement exists in the literature as to proper admission criteria, and, even more so, about the best way to establish them (5). While excellence is considered a prime criterion, the social usefulness of the product is now recognized as an additional key requirement.

2. It controls quality of education in the student years by examinations. Here, similarly, a lively argument prevails among students and educators about the most sensible procedures. All will agree that skill, knowledge, and attitude should be tested in the developing physician with problem solving rather than memorizing the subject of the tests.

3. It sustains training in the house officer years, either as intern or resident, and is increasingly considered an obligation of the medical school rather than of the individual hospital.

4. The medical schools will be increasingly charged with supervising the educational level of the physician after completion of the house officer training to provide a continuum in education (6). The classic postgraduate course by lectures appears to be outmoded, and now other devices are tried such as education of the physician on his own patient or return for a defined period for house officer service periodically after completion of the original organized institutional activity. Relicensing or even recertification by periodic reexamination is under serious consideration, whether or not the original license has been given, shortly after graduation or, as suggested by some, after completion of the specialist training.

The result of these endeavors will be reflected in virtually any health care system by a variety of types of physicians the enumeration of which is almost axiomatic.

1. Primary care or contact physicians, whether they are designated as general practitioners, family physicians, or by various combinations such as general internist-pediatrician or pediatrician/obstetrician.

2. Physicians primarily focusing on the organization of medical care, whether they are called specialists in administrative medicine, community medicine, preventive medicine, or, social science physicians.

3. Specialists in any field, whether it concerns secondary care (which means attention in doctors' offices, outpatient clinics, and general hospitals' facilities) or tertiary care (meaning treatment in specialized units with sophisticated equipment such as intensive care units of various types).

4. Clinical scientists who are giving highly specialized clinical care but who are equally involved in developing new knowledge by research at various levels of complexity, and basic scientists devoting themselves to study in laboratories more or less divorced from patient care.

There is much argument about the level of training at which separation into different tracts leading to the various types is advisable either as a general principle or as a solution tailored to the individual student.

Far more intense are the arguments as to the preferred system of health care in the future. They concern the question of whether practice by individual physicians is today antiquated and can be called a "cottage industry," or whether group practice is preferable. The use of the physician's assistant who, despite a lower level of training, lengthens the arm of the physician has now become a concept accepted only by part of the medical profession and embraced more by persons outside it. We are reminded of the role of the "feldscher" in Russia and the "barefoot" physician in China. However, a democratic system will not accept lower trained physician's assistants as independent practitioners, nor will it be satisfied with the permanency of the lower status. The physician's assistants should thus be members of a team who would make the first contact in the physician's office or at the community health center, but still always be under the supervision of a physician, with two-way radio and television transmission possible at our present stage of technical development. The role of complex health care organizations set up to "blanket the country" like health maintenance organizations or regional medical programs requires testing.

While it is easy to present these problems in sermon fashion, we nevertheless are aware that the medical schools are groping for answers because few firm ones are available today. However, it has been rightly stated that the medical school is more capable of self-reform (7), attempting to answer these questions, than any other part of the university. Indeed, this is the science which we now see, at least in the United States, where many crusaders instead of emphasizing the problems offer easy—but not applicable—solutions. This is easier served by Socratic inquiry as the first way to give answers. This approach is particularly useful in developing the curriculum as the major expression of any answer.

The dilemma is particularly pressing in a new school in which striving for excellence must be combined with maximal flexibility. In the development of such a curriculum, problems, conflicts, tools, and solutions have to be separated. The following enumeration is subjective and many important points may be left out.

Problems

The main difficulties of the curriculum designer are probably the following:

1. *Information explosion.* Knowledge applicable to medicine is accumulating in a greater quantity than the human brain can possibly store. In medicine, particular difficulties arise because

a) in the classic biologic discipline taught before 1960, information is increasing daily;

b) new disciplines like biomathematics, biophysics, biomedical engineering, and genetics justifiably demand great attention in the medical curriculum, and

c) the sociologic disciplines have to be incorporated.

2. *Students' demand for relevance.* Justification for teaching specific biologic facts and principles is requested by the students, and this demand often cannot be fulfilled because experience has taught us that facts considered unimportant to medical management only ten years ago have now had a great impact on our thinking.

3. *Demands of society to fulfill the need of the community for medical care,* leads to diversion of physicians from teaching to service in a university medical center setting. Three communities have to be distinguished:

a) The community surrounding the medical center, frequently consisting of a disadvantaged segment of the society;

b) The total urban, national, and even world community which may want specialized care but also advancement of knowledge;

c) The community represented by the next generation which can request both training of physicians to attend their medical needs and development of new medical knowledge. The requests of this third community are often forgotten today when the emphasis of present medical care shortchanges education from physicians and research.

4. *The rising complexity of medical treatment* increases the cost of both training and medical attention, a problem which is made worse by the worldwide inflation.

Conflicts

Curriculum planning, as an expression of the aspirations and plans of the medical school, requires a decision in a series of conflicts presented by the prevailing circumstances. Some are academic and some social in nature.

1. *Facts vs. principles.* While the practice of medicine, in addition to knowledge of facts sometimes not even explained today, requires the acquisition of these attributes it is rather based on principles which may also apply to knowledge made available in the future.

2. *Research vs. teaching.* This can also be presented as a conflict between clinical science and bedside art. In the care of the individual patient the bedside attention is in the foreground and has to receive emphasis in teaching. However, both prevention of disease and care in the symptomatic stage are based largely on the result of knowledge acquired through research, and efforts to obtain new information are thus to be balanced with demands for clinical care.

3. *Teaching vs. patient care.* The use of patients for teaching medical students and especially house officers often presents awkward problems, particularly with private patients, and especially as manipulative techniques are applied. Experience has taught that the best care is given in teaching institutions, not only because of the availability of techniques and equipment, but even more so because of the particular care that the individual receives in the clinical attention which is part of the teaching effort. The problem, of course, becomes accentuated if the number of patients treated by the institution is so great as to cause a diversion of the teaching effort by inundation with patients rightly clamoring for treatment.

4. *The problems of the individual vs. those of the community.* When, as at present, available resources are limited and the expense of complex treatment becomes staggering, a conflict arises in that a decision has to be made as to who is entitled to a scarce commodity. Secondly, the question is often presented as to whether a potent therapeutic or diagnostic modality benefits the individual or medical science at large. For instance, this arises in organ transplantation and in the application of powerful drugs with a great chance of undesirable side effects. The needs of medical science can be expressed as the requests of future generations. However, it is indeed a thin line between the search for scientific information, which some degrade by calling curiosity, and the actual benefit to future generations.

5. *Episodic vs. long-term consideration in teaching and care* enter into the application of any therapeutic modality when the nature of the long-term effects are frequently unpredictable. But also, the outlook becomes important in the evaluation of the present long-term disease.

6. *Physician vs. governmental social scientist,* a new conflict which is bound to arise with the increasing impact of the government in medical teaching and care.

Tools

In recent years the medical educator has become aware of many possibilities and devices previously not considered which may help in resolving the problems and conflicts listed.

1. *The unity of biology.* Principles and facts learned in lower animals (and even bacteria) may be applicable to man. Equally important is the realization that in the conflict between "interesting" vs. "common" diseases the former may represent a valuable experiment of nature which might help us understand manifestations in the common diseases.

2. *Integration.* This word can be applied to a variety of elements of variable usefulness in medical education:

a) Integration of clinical (and social) with basic science. This is more easily accomplished in the medical student's early years than when the attempt is made to recall basic science information in the later years. Pharmacology, particularly clinical pharmacology, may serve as a useful device to remind the student of basic science principles.

b) Integration of space in multidisciplinary labs which serve as a home base. The teachers go to the students rather than the students going to the different laboratories and lecture rooms (7, 8).

c) Integration of courses in which one organ with its diseases, pathophysiological phenomena, shock, trauma, and nutritional disturbances are taught simultaneously in a coordinated fashion by representatives of each applicable basic or clinical discipline.

d) Integration of different departments when, particularly in the basic sciences, the departmental borders are at present blurred, and, frequently, the same biochemical or biophysical techniques are employed in different departments. The Community Medicine Department is a good example of a multidisciplinary approach in a department.

e) Integration in the students' minds which is the real goal and most difficult to achieve.

3. *Identification of a core curriculum.* The selection of study material becomes more important than ever before. This concerns the teaching of knowledge and skills which every student must acquire and is to be distinguished from the elective or free curriculum which varies for each student depending upon his aspirations and future plans. The student chooses the area of his particular interest which he studies in depth. The definition of core curriculum, however, is the subject for many arguments. A syllabus may provide the best tool for making a core curriculum work since textbooks are hardly available. However, we should underline the attitude toward medicine as a whole and the behavior toward the individual patient. The role of ethics in our teaching and research programs must be considered. It would also be wise to realize that the best researchers and scholars are not necessarily the best teachers. From time to time the teaching faculty should be looked at anew.

4. *Teaching machines, computers, and audiovisual devices* permit the student to study at his own time and at his own speed. This procedure saves faculty time and makes expert teaching available in institutions where particular expertise is not available. Computers in medicine assist not only the teaching devices but offer help today in monitoring treatment, particularly in the intensive care units where various observations are correlated. In addition, they are gradually beginning to acquire usefulness in diagnosis. The desirable synthesis of information by computer is still a task of the future.

5. *Utilization of disciplines on university campuses* that are not offered in medical schools would permit the introduction of social and physical sciences in the medical curriculum.

6. *Outreach into the community* would utilize new resources and aspects of

medical problems which present themselves in different ways from the viewpoint of the University Medical Center (9).

7. *Peer review of medical care and medical education.* It is demanded by society and should become a useful tool in establishing excellence. The new guidelines for accreditation set forth by the Liaison Committee on Medical Education calls for an institutional self-study to analyze the resources available to the school of medicine and the effectiveness of its educational programs by the members of the school's academic community. Such a self-study by faculty, administrative officers, students, members of the Board of Trustees, and alumni of the present status and accomplishments as well as expectations for the future can be very rewarding, for it reveals the strengths and weaknesses in the teaching program and stimulates the desire to achieve the maximum effectiveness.

8. *Educating the public to the problems in medicine.* This is not only the responsibility of the medical school but is bound to become a tool to obtain guidance by the consumer. If society will fully appreciate that training of future physicians guarantees the medical care of future generations and that research, including human experimentation, will improve the health of their children, much of the present opposition of patients' relatives and the community against endeavors of the medical centers will fade.

Solutions

Reorganization of medical teaching, as is the case with all solutions to problems, causes new problems. The four years of study for students must be used to better advantage. Most medical educators have their own subjective answers to the problems and conflicts presented. In this subjective sense, the following three points are being offered:

1. Define and recognize the basic function of a university medical center devoted to improvement and maintenance of health and, with it, the quality of life. This function should include:

a) training physicians together with paramedical personnel, from Ph.D.s to allied health professionals, so that they learn to work together as a team,

b) conducting biologic research as the cutting edge for progres in medicine,

c) developing a scientific method for the best health care delivery system possible, and

d) giving medical care to that segment of the population that participates in the teaching and research effort of the medical center by being the patients—not only in the beds of outpatient clinics but also in the community which is the laboratory for the medical center's community efforts.

2. Develop a new timetable for medical education in view of the great waste of time and duplication in the present arrangements. New proposals are being offered (10). We dare here to recommend that after high school a three-year college course be given including some instruction in the sciences basic to medicine. A three-year course in medical school would follow which, after an initial integrated study of clinical and basic sciences, would consist of

thorough training in the basic aspects of clinical medicine. After these six years, the training as house officer under medical school sponsorship would last for three years in which time would be spent not only in the hospital setting but also in community centers and might include activity in a national health service. Specialization should start only after these nine years following high school education.

3. Mount Sinai has tried to meet the challenge of medical education by announcing almost 15 years ago the Mount Sinai Concept (11). It stressed balance among a) quantitative biology, b) attention to the single patient, and c) care for the total community. This concept still remains our guide in future endeavors.

Today, even in prestigious schools, the trend has turned back to reintroduce the curriculum of the early sixties (12). However, between revolution and reaction, a useful synthesis on a higher level is bound to come.

While it is easy and intriguing to preach possibilities, it might be worthwhile to remember that whatever the solution, it should include two ingredients:

1. Striving for balance with the proper mixture of freedom and discipline.
2. Enthusiasm.

With these ingredients every educational system should succeed. It has been said that some percentage of the students will learn effectively in every system and another percentage in no system; and the real challenge is to reach the group in between.

Finally, I would like to take a subjective look into the future. Medicine in the United States is in a crisis and we cannot predict whether the proposed solutions which include costly national insurance will be successful. Suddenly the government and the population recognize mismanagement and have begun correcting it with radical laws and methods which would be unacceptable in other countries and could not be executed. We hope that the social revolution of medicine will mean improved health care. Two thoughts could serve as guidelines:

1. Real progress in medicine is only in basic research. We recognize the danger of uncontrolled scientific research, i.e., the recombination of DNA whose dangers are being compared with dangers of atomic energy. Despite resistance, a careful solution seems possible.
2. Even more important is the preservation of enthusiasm among doctors despite all difficulties and crises which without doubt will force a solution.

Overview

Today, the situation in medical education seems to be at a critical point with three recent antagonistic developments demanding our attention. In the United States the leadership in medical education is coming to grips with the problems presented by the sociologic revolution in offering a new master plan as a continuum of medical education (10). From China comes the message that a social revolution has effectively reorganized all medical care and thinking and the same is being reported from Cuba (13)—changes which make the demands and achievements of the American social revolution appear insignificant. However, at the same time in this country, a reaction is beginning to set in against the social revolution of the middle sixties. Seymour Lypset is quoted as saying that social "obsessions" last four to five years. The reformer becomes a revisionist in the assessment of change. We might remember that even in prestigious schools there is an impetus to reintroduce the curriculum of the early sixties (12). However, between revolution and reaction, a useful synthesis on a higher level is bound to come.

References

1. Popper, H.: The Role of the Medical School in the Delivery of Health Care, Mount Sinai J Med 40:525–34, 1973.
2. Fuchs, V. R. and Kramer, M. J.: Determinants of Expenditures for Physicians' Services in the United States 1948–68. Commissioned by the U. S. National Center for Health Services Research, Department of Health Education and Welfare. Washington, D. C.: U. S. Govt. Printing Office, 1973 (DHEW Publication No. HSM 73-3013).
3. Perkins, J. A.: *The University in Transition*. The University Press. Princeton, N. J., 1966.
4. Flexner, A.: Medical Education in the United States and Canada, A report to the Carnegie Foundation for the Advancement of Teaching. Boston: The Merrymount Press, 1910. (Reproduced in 1960 by the Foundation.)
5. Ambrosino, R. J. and Brading, P. L.: An Analytical Computer-Based Methodology for Screening Medical School Applicants, J Med Educ 48:332–35, 1973.
6. Kerr, C.: Enlarging Human Capability: The Central Role of the Health Sciences, J Med Educ 47:843–50, 1972.
7. Spilman, E. L.: The Multidiscipline Laboratory, J Med Educ 33:168–74, 1953.
8. Fuhrman, F. A.: Multidiscipline Laboratories for Teaching the Medical Sciences. Palo Alto, California: Fuhrman, 1968.
9. Deuschle, K. W., Bosch, S. J., Banta, H. D., and Dana, B.: The Community Medicine Clerkship; A Learner-Centered Program, J Med Educ 47:930–38, 1972.
10. Evaluation in the Continuum of Medical Education. Report of the Committee on Goals and Priorities of the National Board of Medical Examiners (William D. Mayer, Chairman). Philadelphia: The Board, 1973.
11. Popper, H.: The Mount Sinai Concept, Clin Research 13:500–04, 1965.
12. Goldhaber, S. Z.: Medical Education: Harvard Reverts to Tradition, Science 181:1027–32, 1973.
13. Butler, W.: The Undergraduate Education of Physicians in Cuba, J Med Educ 48:846–857, 1973.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 5, September-October, 1977
Printed in U.S.A.

Health Care Cost Inflation in the United States: Toward a Unified Theory of Cause and Control

S. DAVID POMRINSE, M.D.

This paper will examine the history of the inflation of the major elements of health care costs and seek to demonstrate a common, or at least similar causation for each. Little new data will be offered, rather known information will be reordered. The basic thesis is that, in contradistinction to most fields, effective demand for health care services is determined primarily by the type and volume (supply) of available services and not so much by the sum of individual's needs expressed by their decisions to purchase health services. Obviously, there is a minimum level of health service which any civilized society expects and demands, but efforts to define the volumes of care needed to meet that minimum fail. They fail because of the varying levels of expectations among different cultures and they fail because of the difficulty of demonstrating significant differences in the health status of populations resulting from various increments of personal health services. Thus, the cost/benefit ratio of any service appears almost to be irrelevant to individuals and those who act on behalf of large groups. Compounding all of this is the lack of good measures of the effectiveness of various services (with the exception of the death rate) in terms which can be translated into economic benefit. Thus, there are no population-based data showing various degrees of disability following one or another method of providing health care. We know only what it costs, not what it did. And with costs escalating rapidly to the point where they squeeze the dollars available for other human wants, the health field is less and less able to document its value and is increasingly subject to criticism as "wasteful, out of control, inefficient," when the roots of the problem run much deeper than suggested by newspaper headlines. They must be traced by examining each of the three main ingredients in health care (manpower, institutions, money), how and why their costs are inflated and the compounding effects of these changes on the percentage of the gross national product expended on health care service.

Manpower

We will refer here primarily to physician manpower, although similar comments can be made regarding dentists, nurses, social workers, therapists, and technicians. During the 1930s, physicians did not command the high economic position they do now, the median physician income being in the top

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From the Office of the Executive Vice-President of The Mount Sinai Hospital and The Mount Sinai Medical Center, New York, N. Y. 10029.

Requests for reprints should be sent to: S. David Pomrinse, M.D., Executive Vice-President, The Mount Sinai Hospital and Medical Center, Fifth Avenue and 100 Street, New York, N. Y. 10029.

1 percent of incomes in the United States. Since the population was poor and governmental programs minimal, they got along without all but the most essential health services with a consequent reduction in the demand for physicians. Apocryphal stories are told of doctors driving taxicabs. During World War II, a large fraction of physicians joined the armed forces to care for the healthiest people we could recruit or draft, leaving behind a far smaller number of doctors to care for the same number of the aged, chronically ill, acutely ill, and the children. America learned about doctor shortages in a hurry. By the time physicians returned from the war, specialty boards were flourishing. Doctors being intelligent and having had their life patterns disrupted by the war, recognized the value of qualifying as a specialist and took the required residencies. The very fractionation of the physician led to his perceived nonavailability. The public "couldn't find a doctor" because the prewar general practitioner was now a dermatologist. Physicians moved increasingly into specialties.

At the same time, an explosion of medical information was becoming available, funded mostly by research grant funds from the National Institutes of Health. This gave even greater validity to the move toward specialization and, in the medical schools, caused the status of the researcher to be raised. Prewar, the research physician pleaded for funds; now he brought to the schools large amounts of money that somehow found their way into supporting medical education. Students modeled themselves on the successful researcher, and tended to follow in his path, thus reducing the numbers of M.D.'s who might have been available to the general public as practitioners. During the 1950s, the U.S. Public Health Service, recognizing that no new medical schools had been started in 30 years, calculated MD/population ratios for the next several decades and showed an increasing deficit of physicians. These data, plus the general awareness of a physician shortage, led to enactment of laws in 1963 and thereafter that helped create 20 new schools and doubled the number of graduates in the last decade. While many of these graduates have not yet entered practice, it seems clear that they will do little to ameliorate the remaining shortages in central city and rural areas for both the obvious reason that a physician must earn a living and if the population is too poor to support him, no doctor (barring a few zealots) will settle there and the less obvious reasons of professional interaction with his peers, status, hospital affiliations, etc. However, for most of America, the next decade should see a sharply increased availability of physicians.

When a doctor opens a practice, he becomes an available source of supply. While seeing his first few private patients, he is likely to lean over backwards to be careful, to be sure he has not missed anything, that nothing untoward develops between visits. He orders tests and recommends revisits — and they get paid for by the patient or his insurer and the volume of services per 1000 population increases. He discovers that this mode of practice is helpful in avoiding malpractice suits, is looked upon by his patients as expressing concern for their problems and is economically rewarding in the fee-for-service system. Since all physicians are exposed to similar pressures, the standard work-up becomes the accepted mode and becomes codified into hospital and professional society rules.

The basic point is that volumes of services engendered by individual physicians can be controlled by elaborate, expensive policing mechanisms but the simplest and surest way to control them is to limit the number of physicians. If the "mix" of physicians moves more toward general internists, pediatricians and family physicians and away from surgeons, the population will still have adequate availability of a physician but the gross economic impact will be reduced. Generalists, in our value system, earn less than surgeons so that we get a compounded result – fewer total physicians, fewer of whom command very high incomes.

The time has come to reexamine our inducements to expand medical schools and to encourage the creation of new ones with their attendant need for associated high-cost tertiary care hospitals. We must remove the opportunity for Americans studying medicine abroad to be brought into the mainstream of American medicine. A national consensus decision now needs to be made that not every mature, bright young person who wants to should be permitted to become a physician and at the same time that not every crossroads will have a doctor in residence. One of the prices we shall have to pay to control health costs is a slightly reduced number of physicians offset by a better distribution of specialties. It has been estimated that every physician that enters practice adds $250,000 to the cost of medical care. Controls on the physician may reduce that slightly, keeping him from going into practice eliminates it altogether.

Institutions

A not dissimilar history pertains to hospitals. The lack of capital during the depression kept new construction to a minimum and the requirements of World War II brought new hospital building to a virtual halt. The problems associated with an aging national hospital plant and the beginning redistribution of the growing population to the suburbs led to a national recognition of the need for new construction. Passages of the Hill-Burton Act in 1948 helped fuel an explosion in new plant building and the new beds were used; studies by Roehmer show that within very broad limits, occupancy stays constant. However, the politically devised formula for the allocation of Federal funds encouraged the creation of large numbers of new hospitals in rural areas at a time the farm population was decreasing and permitted only minimal investment in center city hospitals, many of which were, and still are seriously obsolescent. During the 1950s it began to be realized that just building beds would not solve the medical care needs of the country and it is interesting to note that the peak beds/1000 population ratio was reached in 1955. The need to slow capital investment in new beds was translated into action with the passage in New York State in 1963 of the Metcalf-McClosky Act which was the first legislation to require planning approval. This has now spread nationally, culminating in the 1975 National Health Planning and Development Act.

Nursing homes, aside from some large country doctor or church-supported institutions were either small and reserved for the wealthy or moderate in size and served as dumping grounds for the elderly poor. The major thrust leading to growth in this segment was the Kerr-Mills bill in 1968 which provided for payment to the institution rather than to the recipient of welfare, followed in 1965 by the Medicaid program. Today, Medicaid payments to nursing homes exceed those to hospitals.

Again we see a pattern of a perceived deficiency reacted to by government without regard to how much the operation of the beds would cost. A need was seen, an estimate of required capital made and accepted, but no recognition of the longer term impact of the investment was considered.

What can be done? If spending on hospitals and nursing home operations is to be cut with consequent rationing of care, the choice lies between reducing funds available to all hospitals or maintaining some and closing others (the major economy comes from total closing, not just shutting down a few beds in each hospital). Can the country live with fewer beds? With a national occupancy figure of 73 percent, and a general recognition that efficiency peaks at 85 percent, it seems clear that some 10–15 percent of the beds in the country could be closed. Depending upon which hospitals are selected for closing, patient inconvenience should be minimized. Physicians will have to be accommodated on the staff of the remaining hospitals. Total employees in hospitals will be reduced, causing serious local unemployment problems, but since two-thirds of a hospital's expenditures are for payrolls, there is no other way to reduce spending significantly.

Why not simply reduce all hospitals' income across the board? Unquestionably, there is some inefficiency in hospital operations—just as there is in private industry and in government. The savings to be obtained from reducing inefficiency are trivial compared to that obtainable by closing hospitals. Is it not better to have fewer, well-run, capable institutions organized in accordance with a community-accepted plan, than a larger number of inadequately staffed hospitals operating at marginal levels of safety and patient satisfaction?

So far, this paper has argued that overinvestment in manpower and in facilities is at the root of the inflation of health care costs. But the medical care cost index is increasing at a rate far greater than the annual net increase in manpower or hospital beds. So let us now look directly at the resource which is measured by the inflation rate of money.

Money

The methods for paying for medical care, especially for large bills, has undergone a revolutionary change in the last 40 years. Originally paid for directly by patients, 80% of hospitals bills are now paid for by third parties. While governments at all levels have long operated health facilities for certain classes of patients (poor, insane, veterans), the growth of third-party payment can be said to have emerged as a major force during the Depression with the growth of Blue Cross into a national program. Major impetus to having someone other than the patient pay for care developed during and after World War II when fringe benefits were excluded from wage controls. Coverage quickly spread to cover almost all the regularly employed for hospital care and a major segment of the population for surgical and medical benefits. The final major thrust was given by the passage of Medicare and Medicaid in 1965. Now the bulk of large medical bills were not paid for by the patient—the premiums were paid by employers largely or were hidden in taxes in the public programs. At the same time, people felt (and were so encouraged by their labor leaders) that they had a right to use their benefits—and so they did. There was a divorcement between the decision to seek care and the concern about its cost. "The best there is, and money is no object" became operational terms.

Aided by retrospective payment formulas for hospitals and usual and customary fees for physicians, change levels were effectively set by the sellers with little the buyers could do about it. Hospital unions quickly took advantage of the pass-through of costs and were able (abetted by governments and hospital boards unwilling to face a strike) to escalate working pay from substandard to the highest for comparable jobs. Physicians demanded and got the newest technology in the absence of countervailing financial or regulatory pressures. Regulatory agencies demanded ever increasing standards of "quality" at ever higher cost. Money was no object until the total amounts spent threatened profit margins of industries and forced priority decisions by state and local governments which they found intolerable. Pressure for reducing the inflation rate of health costs have mounted and cannot be ignored.

What can be done? As with manpower and facilities government recognized a real need to keep people from being wiped out by a large hospital bill or being denied care. But, the solution carried the seeds of its own destruction and the pendulum swung too far—from having done too little to trying to do too much. If fewer dollars are to be spent, inflation will be controlled only by reducing the effective demand for services. Demand does not equate with need. Many visits to physicians and some hospital days are not "needed"; their absence will not make people sicker. There is no evidence that most "preventive" services in adults are effective. To avoid these services, a form of rationing must be reintroduced. Patients must be faced with the same economic discipline they face in all other decisions: Can I afford it? Do I want it more than something else? And the way to balance provision of needed services with an economic interest in those to be received is to require the patient to pay part of the bill from his own pocket. Deductibles high enough to avoid the excessive cost of insuring small bills and co-insurance requirements of 25 to 33 percent on larger bills. However, to avoid serious economic damage from health services and to assure that needed care will not be foregone, these must be coupled with a "catastrophic illness" provision, sharply reducing payment by the patient once he has spent some given (10 to 15 percent) percentage of his annual income from his own resources. In other words, we should dampen the demand for first-dollar coverage to reduce the total volume of services but avoid major economic insults arising from illness.

It is recognized that a program such as this, mandated by legislation, would increase administrative costs and bad debts for hospitals and would cause physicians difficulty in ascertaining whether the patients expenditure requirement had been met—certainly, a means that is not a popular device; however, it would only come into play for the small (2–3%) proportion of the population incurring large bills.

Conclusion

The need to reduce effective demand for medical care if the inflation in cost is to be reduced has been shown. The development of the excessive capital investment in manpower and facilities has been traced and suggestions for reversing these trends made to the end that this reduction in supply will help to reduce demand. A scheme for reinvolving patients in the economic effects of their demand for care has been offered. The public debate must now center on whether the country is really serious about stopping the rise in health care costs at 8.5 percent of GNP and, if so, whether it is prepared to pay the political price resulting from medical school and hospital closings, and the institution of financial penalties. We can have a healthy medical care system in this country, but the price must be paid.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 5, September-October, 1977
Printed in U.S.A.

Clinical Research and Teaching in the Academic Medical Center

THOMAS C. CHALMERS, M.D.

A common dictionary definition of research is: "1) careful or diligent search; a close searching; 2) studious inquiry or examination; especially critical and exhaustive investigation or experimentation having for its aim the discovery of new facts and their correct interpretation, the revision of accepted conclusions, theories, or laws in the light of newly discovered facts, or the practical applications of such new or revised conclusions, theories, or laws" (Webster's Third New International, Unabridged, 1971). According to this definition the physician is conducting a research project every time he diagnoses and treats a patient. The taking of a history and conduct of a physical examination – to be successful – should be a studious inquiry and a critical and exhaustive investigation. The ordering of laboratory workup in an economic and efficient manner is experimentation for the discovery of new facts. Prescription of therapy is the practical application of new facts, and to make the treatment effective it must be tailored to the individual according to the correct interpretation of the material gathered. If the physician is not alert to the need to revise accepted conclusions when the facts warrant it, i.e., to conduct experimentation in his daily practice, his patients will suffer. This reasoning assumes, however, that in acting on the data he gathers he will have confidence in the reliability of that data and in his skill in sorting it and drawing the proper conclusions. In other words, the physician must be trained in the disciplines that are the prerequisites for the conduct of good research.

The academic medical center is the ideal place in which to have a serious illness for several reasons which will be discussed in some detail in this paper. They have to do with the fact that the research required to practice good medicine is of a higher quality when fully supported by modern facilities and trained people, and the application of that research to the routine care of patients is best maintained at a high quality when students at all levels of their education and training are in constant attendance. Students are quick to recognize incompetence and to challenge decisions that are based on poor research or improper interpretation of good research. The academic milieu that medical schools and their teaching hospitals must strive for is one in which the facilities are available to gather all the information necessary to treat the patients properly and to teach students how it is done. Sometimes the information comes from discussion and analysis of the world's literature;

From the Office of the Dean, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Requests for reprints should be sent to: Thomas Chalmers, M.D., Dean, Mount Sinai School of Medicine, Fifth Avenue and 100 Street, New York, N.Y. 10029.

sometimes the latter is totally inadequate, and it must come from original research performed at the institution. When the latter occurs and has a successful application to the saving or betterment of a life, those involved have the highest conceivable stimuli to excel in their future clinical efforts.

The Mount Sinai School of Medicine was structured on the base of a respected and excellent teaching hospital as a further expansion of the concept that research, teaching and patient care each have an equally important and beneficial effect on the other. The best patient care occurs in the places where the best teaching and research are going on; the best research related to patient care occurs in the places with the best patient care and teaching; the best teaching occurs where the patient care and research are exemplary. Efforts to maintain excellence in any one of the three will have an influence on the others, and must take the close interactions into account. Slippage from excellence in any one of the three will seriously affect the other two.

Changes at Mount Sinai since the Medical School Was Added

In 1968 students were admitted to the 1st and 3rd years of the Mount Sinai School of Medicine. At that time the school budget was around $2.6 million, and the institution was receiving $8.3 million in extramural support for research, and was spending $1.7 million of its own for research purposes. Eight years later, in the academic year '75–'76, the budget of the school was $10.4 million, and the institution was receiving $17.7 million in extramural support for research, and total support of research was $21.1 million. There was thus more than a doubling of expenditures of both extramural and intramural support for research. There was a sharp increase during 1975, when the Annenberg Building became fully operative, and the school and hospital expanded its square footage for research from 146,000 to 460,000.

The best evidence of increased research activity is the number of papers published in the scientific literature, which increased from 600 in 1968 to 1150 in 1975. The number of faculty listed as authors on these papers increased from 470 to 1431, a reflection of a common national trend toward multiply authored papers, but also a clear indication of active involvement in research of 14/17 of the faculty. In 1968 470 of the 867 faculty were listed as authors of research papers, and in 1975 the ratio was 1431 out of the 1739 total members of the faculty in the school. These figures include full, part-time, and voluntary faculty, and include all of the affiliated hospitals.

So, there is ample evidence of a sharp increase in research activities at Mount Sinai since the start of the school. The student body has increased from 60 in the 1968–69 academic year to 383 in the 1976–77 academic year. There are now 110 students acting as third-year clinical clerks, and 91 fourth-year students. There is thus a sharp increase in teaching activities.

In the assessment of the interactions between teaching and medical care in the academic medical center, basic science departments are an important consideration. There is no need any more to justify basic research as necessary for appreciable advances in medical care, and for the adding of essential background to general medical knowledge. In addition, it is apparent at Mount Sinai that the basic science departments are contributing to the quality of the clinical teaching, patient care and research. In the first place there is a geographic proximity that is rather unusual in medical schools. The clinical and basic science departments are closely intertwined in the Annenberg Building. The personnel travel in the same elevators, eat in the same dining room, use the same library as the clinicians. There is bound to be profitable interchange of knowledge and ideas for further investigation and teaching. All meetings of the chairmen of the departments of the medical school are combined meetings in which the basic scientists and clinicians can exchange their views. Hospital-oriented working committees usually have a basic scientist as a member, and vice versa. Search committees have a healthy mixture of both. So, the opportunities for interaction are many.

Another stimulus toward better patient care and teaching in the academic medical center is the convenient availability of research laboratories for the clinical departments. The many laboratories that were occupied by school personnel in the hospital proper before the opening of the Annenberg Building are still available for clinical research. In addition, about half of the top 18 floors of the Annenberg Building are occupied by investigators and teachers in the clinical departments. These are thus in close proximity to the emergency rooms and ambulatory care facilities in the basement and first four floors of Annenberg.

The cardiovascular center on the Eighth Floor of Annenberg is a good demonstration of the spatial interaction between patient care, teaching, and research in the modern tertiary care hospital. It contains the cardiovascular surgical operating rooms, the recovery room, and a coronary care unit for the more severely ill patients. Associated with these patient care facilities are combined research and patient care laboratories such as those for cardiac catheterization, ultrasonography and related cardiac physiologic procedures. There are also a number of contiguous classrooms and offices, offering plenty of opportunity for interaction among the surgeons, cardiologists, and their students.

Although the steadily increasing value of research grants awarded and the ever enlarging number of papers published in reputable scientific journals indicate an expanding scientific expertise at the medical center, how does one know that this is having a favorable influence on the teaching of medical students, house staff, and attending physicians, and on the quality of patient care? Indirect measures of the former are the observation that Mount Sinai graduates seem to be obtaining postgraduate training in better and better teaching hospitals, and the Mount Sinai clinical services seem to be attracting better and better graduates of other medical schools for training at Mount Sinai. These signs of quality, however, are difficult to measure.

Even harder to measure is the impact of the move from a hospital to an academic medical center on the quality of patient care. It may be assumed that patient care will be better if the better graduates of Mount Sinai and other medical schools are joining the staff for postgraduate training and staying on to practice and teach on the faculty. But this observation is a measure of the process, not of the outcome. The essential question is whether or not the patients receive better care.

The most difficult measurement of all in medicine is that of output—quality of the patient care delivered. Is this better on the average in an academic medical center than in a general hospital without an attached medical school? The answer is made nearly impossible to obtain by the fact that outcome is determined by two equally important determinants: severity and complexity of illness at the time of the patients' admissions to the medical care facility, and the quality of the treatment administered. The former is impossible to control so that the latter can be accurately assessed. It stands to reason that the more physicians graduate from an institution's undergraduate and graduate programs and the more its research results become known, the more there will be a tendency in the community to send the more difficult cases to the institution.

As a result of these factors, the academic medical center may well have a longer average stay in the hospital and may even have a higher death rate for specific diseases. If the treatment were not superior, the stay might be even longer, and/or the death rate higher.

Satisfaction of patients and relatives is also not necessarily a reliable index of outcome. A milieu of sicker patients may lead to more complaints. The only measures presently available which might be applicable are the compilation of untimely or unnecessary deaths, or of complications that might be the result of inadequate attention to detail. Even these could be influenced by admission policy.

The complaints of patients or relatives about the quality of care are bound to have an influence on those working in the academic medical center. This is especially applicable to the niceties of care, the compassion and politeness of those directly caring for patients. Sometimes patients may suffer from too frequent or insufficiently gentle examinations by students or physicians in training. Sometimes mistakes are made by inadequately supervised trainees. Similarly there are unfortunate mistakes and discomfort related to research just as to patient care. These disadvantages must be weighed against the advantages of frequent observation and discussion, when compared to the relative neglect typical of the hospital without physicians in training and clinical research. The relative benefit-to-harm ratio is the result of the mean effects of many factors, and although it may be hard to prove, the academic medical center is on balance the place to be when the illness is complicated or severe.

In the final analysis the only measures of quality now available which do mean something are the opinions of professionals who work in or refer their patients to the institution as well as others, and can make some rough comparative value judgments.

There is a potentially exciting approach to high quality medical care that Mount Sinai has just begun to explore, but the payoff is a number of years away. At the present time the quality of care in an institution depends primarily on the quality of the clinical judgment of its professionals. An early correct diagnosis is more likely to lead to early and expeditious correct treatment. Proper treatment depends on a clear understanding of pathophysiology and of the randomized controlled trials evaluating specific therapies. The discipline that is most ubiquitous in the proper solution of all of these problems is biostatistics. Next in the line of development and application is computer science, or artificial intelligence. Diagnosis in clinical medicine depends on the remembering of enormous amounts of data collected in the past and on the processes of multiple variable analysis in interpreting those data. The disciplines of biostatistics and the techniques of computer science are crucial to the ideal carrying out of these tasks. Medicine is still a long way from using them in the optimal way, but that time will come. In an effort to hasten it, Mount Sinai School of Medicine has a Department of Biostatistics that will be funded fully as well as biochemistry or other basic sciences, and an Institute of Computer Science that likewise will be as well developed as the basic sciences departments. It is anticipated that when medical students are graduated that are well educated in these disciplines, the full use of the available techniques for storage and analysis of clinical data will result in a quantum leap in the quality of medical care delivered. The academic medical center that Mount Sinai has become may well lead the country in this regard, and when that happens great thanks will be due to Joseph Klingenstein and Gustave L. Levy for starting it all.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 5, September-October, 1977
Printed in U.S.A.

The Program-Resource Concept: A Management Approach for an Academic Health Center

SAMUEL DAVIS M.S.* AND WILLIAM D. CARSWELL, M.S.I.E.†

The rapidly increasing size and complexity of the modern hospital and medical center have made the classic managerial functions of planning, operating, and controlling more difficult to perform, yet these functions are essential to the stability and growth of the organization. Most traditional, functional organizational structures have evolved to a point whereby effective management of the organization's resources is hindered, if not made impossible, because of reliance on personal experience and knowledge, of the structure and dynamics of the organization for success in decision-making.

What is needed in today's hospitals is an underlying science, or at the very least a more structured, less personified approach to organization and management. This kind of philosophy has been loosely termed the "systems approach."

The systems approach is primarily a way of thinking about the job of managing. It affords a framework for integrating into a whole the internal and external environmental factors and the diverse operations that affect the success of an organization. It recognizes subsystems within which the manager must operate. The systems concept advances a way of thinking that helps to explain some of the complexity of the manager's environment and also assists the manager in the decision-making process.

Although the adoption of systems theory in hospital management is a fairly recent development, this trend is likely to accelerate. More and more hospitals are beginning to realize the importance of such an approach and the need to redesign their organizational and managerial systems for decision requirements. This evolution of management style has necessitated the development of a different type of manager, a generalist who understands mixed disciplines and the need to relate diverse operations and specialties toward a defined systems purpose—in hospitals, the efficient and effective delivery of health services to appropriate target populations. It is becoming increasingly important that today's hospital manager understand and practice the fundamental tenets of the systems approach.

The authors' experiences in large institutions and now at The Mount Sinai Medical Center in New York have reinforced the conviction that hospital organization and management as we generally observe it is not likely to continue in its present functional form. This disparity between traditional organizational/managerial style and the need to define and accomplish institutional purposes has required a comprehensive reorganization of Mount Sinai's operation.

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* Director of The Mount Sinai Hospital and Senior Vice-President of The Mount Sinai Medical Center, New York, New York; Associate Professor of Administrative Medicine, Mount Sinai School of Medicine of The City University of New York, New York.

† Senior Consultant, The Mount Sinai Hospital, New York, New York.

Requests for reprints should be sent to: Mr. Samuel Davis, Director, The Mount Sinai Hospital, Fifth Avenue and 100 Street, New York, N. Y. 10029.

Editor's Note: This article is based on a previous article and has been specially edited for inclusion in this issue because of its pertinence.

This program restructuring at Mount Sinai is now underway and is enhanced by the introduction of various management science disciplines and methodologies. The intent of this paper is to present our viewpoint for integrating various organizational and managerial techniques to achieve an effective system for managing hospital operation. We do not contend that the particular systems approach to management as defined at Mount Sinai is the only road to effective management, but we do believe that the particular organizational structure proposed, supported by suitable management techniques, is a realistic system for effective hospital administration.

We feel such an approach is not only appropriate for a 1200-bed medical center hospital such as Mount Sinai, but is totally applicable and necessary for any size hospital or health care institution. Specifically, we will show how the program-resource organization structure, various planning and budgeting methods, and an appropriately designed management information system (MIS) are integrated to provide the decision-making capabilities required in the environment of the modern hospital.

Organizational Structure

The increasing complexity of modern hospitals, combined with adherence to the hierarchical, monolithic organization is viewed by several writers as an underlying deterrent to effective management (1, 2, 3). Without an organizational structure that reflects the goals and philosophies of a complex institution, there is little possibility that a manager can successfully direct the activities of that institution.

Today's hospital environment requires an organizational structure that simultaneously accounts both for the collegial, participatory decision-making structure for directing health professionals and the hierarchical, centralized decision-making structure for managing unskilled workers (2). This structure has been termed a 'matrix organization.' Such an organization is shown in Figure 1, that of The Mount Sinai Hospital.

On the horizontal axis of this matrix are those managers who control institution resources—its personnel, matériel, spaces, and finances. These managers include the directors of nursing, support services, personnel, and finance. On the vertical axis are the physician-managers who control the institution's programs—typically separated into Medicine, Surgery, Psychiatry, etc. The importance of the program dimension in management is particularly relevant in teaching institutions, where the actions of full-time medical staff directly influence the use of the hospital's resources.

At Mount Sinai we have implemented the program-resource concept, a form of matrix organization. Under this system of management, almost every hospital employee serves two designated "masters," one for program function and one for resource function. This allows the hospital employee to have dual identification. Through the program resource concept, the senior clinical

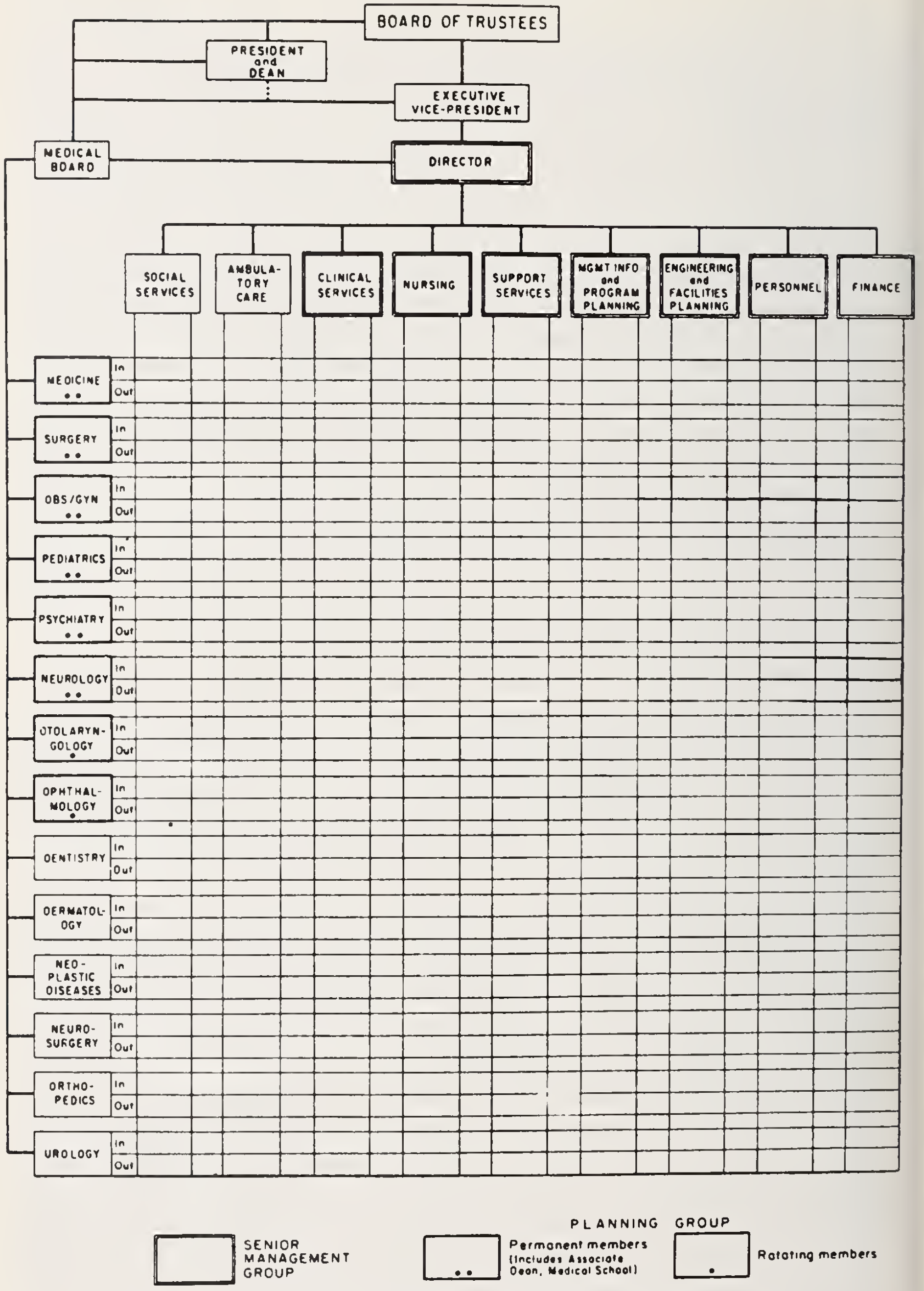
BOARD OF TRUSTEES
PRESIDENT and DEAN
EXECUTIVE VICE-PRESIDENT
MEDICAL BOARD
DIRECTOR
SOCIAL SERVICES
AMBULA-TORY CARE
CLINICAL SERVICES
NURSING
SUPPORT SERVICES
MGMT INFO and PROGRAM PLANNING
ENGINEERING and FACILITIES PLANNING
PERSONNEL
FINANCE
MEDICINE
SURGERY
OBS/GYN
PEDIATRICS
PSYCHIATRY
NEUROLOGY
OTOLARYN-GOLOGY
OPHTHAL-MOLOGY
DENTISTRY
DERMATOL-OGY
NEO-PLASTIC DISEASES
NEURO-SURGERY
ORTHO-PEDICS
UROLOGY
In
Out
SENIOR MANAGEMENT GROUP
PLANNING GROUP
Permanent members (Includes Associate Dean, Medical School)
Rotating members

FIG. 1. The Mount Sinai Hospital Table of Organization, January 1976.

nurse is able to identify not only as a member of the program department, but simultaneously as a member of the nursing profession. Similarly, other health resource personnel are able to identify both with their profession and with their treatment team.

The basic functions of a resource-department head are to recruit and hire personnel, train them in the discipline of the department, assign them to program responsibilities, supervise their work within the discipline, evaluate and promote them within the discipline, and dismiss those whose performance is unsatisfactory. The resource-department head also serves as a consultant in his/her discipline to the program directors.

While resource-department heads have responsibility for setting objectives that relate to their own disciplines and for the resources for which they are responsible, program directors also are able to function effectively under a system of management by objectives. Each program director must develop a general statement of objectives for their program. The measure of their performance is how well they achieve stated objectives. If resources are committed to the program consistent with those objectives, they are obliged to carry out the objectives. If resources cannot be committed, they may reduce program objectives in scope and content. Thus, the program-resource concept establishes a clear basis for organizational accountability and the development of measures of performance.

Under the program-resource concept at The Mount Sinai Medical Center, the President/Dean and his advisory group recommend broad hospital objectives. The overall program determination and the recommendations to the Board of Trustees for program priorities are their primary responsibilities. Under this system, the hospital director has two basic responsibilities: to answer to the governing board for the effective use of the hospital's resources, and to serve as a consultant to the President/Dean, Executive Vice-President, and program directors concerning application of the management process to achieve the hospital's and medical center's objectives. In this regard, the hospital director helps to define programs, to determine the necessary resources, and to develop targets and effectiveness measures on how well the program goals have been achieved.

In the program-resource concept at Mount Sinai, the principal organizational objectives are set forth as programs, and resources are identified as serving those programs. By such devices, problems of employee identification are addressed, cost control and program budgeting are made possible, task specialization is rationalized, and, most important, scarce health personnel have time to do the work for which they were trained. The measure of effectiveness of this organizational approach is whether, indeed, program outputs or purposes do improve against the agreed upon target of program performance. The program-resource concept is one solution to the problems of complex medical care organization.

We have described both the beginning and the end point of most program resource or matrix reorganizations in hospitals. What will typically remain unchanged are methods of planning, operating, and controlling that must *support* the program-resource organization philosophy. Specifically, we will discuss how, at Mount Sinai, program planning and budgeting, zero-base budgeting, financial modeling, and a management information system are integrated to sustain the organizational and managerial structure.

Planning and Budgeting

The public's awareness that it is paying greater amounts for health care has dictated that management techniques for accountability be developed. The program-resource concept makes possible accurate cost analysis and cost control through application of program planning and budgeting. That is, the resources required to meet program objectives—personnel, money, matériel, and facilities—should be planned and budgeted to reflect the cost of each program at its inception and annually thereafter. Departmental budgets also should be prepared to reflect the allocation of its resources on a functional basis and to meet the requirements of uniform accounting, particularly third-party reimbursement. Such budgets also provide a valuable management tool to the department head and to the hospital administration.

As applied at Mount Sinai, the program-resource concept will result in two complementary operational budgets, one showing the cost of the resources, the other the cost of each program. If the resources used in each program are allocated properly, their cumulative costs will equal the overall program cost. Organizational accountability and responsibility for manpower costs can thereby be appropriately assigned.

Program planning and budgeting in itself will not control the spiraling costs of operating a modern hospital. It is a tradition firmly based in virtually all health care institutions to sustain all operations at current activity levels for the next budgeting year and to consider in depth only those new operations that will compete for the institution's resources. Inherent in this budgeting scheme is a yearly quantum jump in the bottom line of the institution's operation. Even if a revenue or expenditure ceiling is known in advance (which is not commonplace), the trade-offs among programmatic activity cannot be objectively negotiated without serious harm to the administrator-program director relationship.

There is, however, an approach developed by Peter Pyhrr (4) called zero-base budgeting which addresses many of the problems encountered in traditional budgeting. Simply, the concept is to identify and define programmatic activities, categorize and describe programmatic activities in "decision packages," analyze and reduce or augment these packages, assign a priority to them, and finally apply the estimated revenue (or expense) ceiling to determine those that are to be included in the budget and those that cannot be included.

Because the zero-base approach delineates and analyzes each discrete activity in the hospital, it not only provides detailed budgetary input, but also specifies activity objectives, resources required, alternative modes of activity considered, and performance measures for subsequent operational audits. This approach is consistent with the management by objectives philosophy *and,* at Mount Sinai, provides a base for implementing routine management reporting on program and resource performance.

The advantages of the zero-base approach over traditional budget cycling are well-documented by Pyhrr and others. The most important attributes realized in our approach at Mount Sinai include its ability to: spotlight activity redundancies, specify program priorities, allow interprogrammatic comparisons, focus on whole programs rather than program marginal increases, and avoid budget recycling when revenue or expense ceilings change. However, program budgeting and zero-base methods are not easy to implement. Much consideration must be given to potential disaster as a result of insufficient indoctrination and inadequate process definition. But, a well-planned and designed budgeting system can provide the vehicle objectively to meet institutional goals and simultaneously to avoid constant disparities in bottom-line revenues and expenses.

How can bottom-line revenue be determined for the forthcoming budget year? Mount Sinai is now integrating a financial planning simulation model with the program/zero-base budgeting approach described above. This modeling capability will allow for an iterative process of program structuring and revenue optimization. That is, the expected revenue for a mandated base of programs will be derived from the model simulation. As "optional" revenue- and nonrevenue-generating activities in order of priority (as derived through the zero-base process) are incrementally added to that base, a revenue sensitivity is noted. Trade-offs among the program decision packages can then be made to optimize the use of anticipated revenue generated by the mix of program activity and supporting resources. This approach not only avoids deficit spending but also provides a methodology for achieving institutional goals in the most cost-effective manner.

To this point we have discussed how the program-resource organization concept and the requisite planning and budgeting techniques are being developed and implemented at Mount Sinai Hospital. However, this or any organizational and managerial framework depends on a Management Information System (MIS) that is responsive to the various needs of managers in all phases of planning, operations, and control. The MIS is the basis for any effective management structure. As such, we have offered an overview of MIS attributes and some recommendations for its development.

Management Information System

"Information systems" and "management information systems" have only recently become accepted parts of our vocabulary. However, the understanding of their meaning has not corresponded to the word's increased usage.

An information system is the procedure or mechanism whereby numeric, alphabetic, graphic, photographic or other information is gathered, stored, perhaps rearranged, and retrieved. A *management* information system provides such information in various formats and detail levels for purposes of decision-making in the management functions of planning, operations, and control.

In addition to merely providing appropriate data to which the manager might refer as he or she makes decisions, a true MIS also directly supports and assists the decision-making process. Where the typical information retrieval system might only provide a historical record, the MIS can highlight exceptions, predict consequences of alternatives, or even prescribe optimal courses of action. For example, at Mount Sinai, the MIS provides, among other uses, various managerial levels with appropriate productivity reports in which actual performance is compared to predetermined standards, workload forecasts are derived for future periods, and employee work schedules are generated which match available personnel with anticipated workloads.

To make the hospital more manageable, particularly in the program-resource organization which expands informational needs, we must design, implement, and utilize better management information systems. Information and its use in the decision-making process is not only a prerequisite but is in general *the* prerequisite for good institutional management in the health care field.

The needs for management information systems can be expressed in terms of the three principal functions of management—planning, operations, and control. These are summarized below in an order that facilitates our presentation.

Controlling is the process of assuring that the functions being managed are adhering to an agreed-upon plan and are achieving predetermined objectives. Clearly, the key ingredient for successful control is the feedback of suitable information in a format which allows corrective action. Upon reflection, it is rather easily seen that the characteristics of a good control system are virtually equivalent to those of a good management information system. That is, managerial control will be enhanced as MIS is enhanced. The two are almost synonymous.

Planning includes such activities as assessment of current and future demands, evaluation of alternative courses of action, specification of those programs and systems which are to be undertaken, development of program objectives and criteria for success, and the budgeting process. These are not independent activities.

The attributes of the MIS are ideally suited to gather, analyze and structure the kind of data base required for program and resource planning. The properly developed MIS should provide a mechanism to relate resources to activities, i.e., to convert various alternative programs or program activity levels to resource requirements. Thus, the MIS not only supports both the control function and the planning function, but it also serves as the link to tie the two functions together. The control (feedback) system provides cost-effectiveness productivity information to feed the planning process; and planning develops the standards and expectations used by the monitoring component of the control process. The only conclusion that can be drawn is that without MIS there is not adequate management planning or control.

Operations includes those day-to-day activities necessary for organizing and directing hospital processes. Since the hospital is such a labor-intensive "business," operating 24 hours a day for seven days a week, and responding to demands which are in part unpredictable, the most important operational management activity is that of personnel staffing and scheduling.

The types of management information required to support personnel scheduling and other operational functions are not unlike those for planning and control. However, routine operating decisions require a more sophisticated MIS in terms of timeliness and detail. The added costs associated with such enhanced day-to-day decision-making capabilities are significant, but not of the magnitude of the costs intrinsic in inefficient trial and error personnel scheduling methods now in general use. Without this operational component of MIS the potential benefits of the planning and control MIS functions cannot be fully achieved. It is only through a fully integrated and sufficiently detailed MIS that the real advantages of such a system may be realized.

We have indicated above the general needs a hospital MIS must adequately address. In developing such a system at the Mount Sinai Medical Center, we have identified and will be implementing certain strategies of MIS design necessary to support a program-resource organization. The following are recommendations that we feel are among the most critical.

—The management information system is not a separate system to be added to the top of the traditional information systems. The MIS must be fully integrated with the general accounting system, patient accounting, personnel/payroll, statistical reporting, inventory control, census, and the like.

—Remove the data processing department from the exclusive sphere of finance. Our recommendation merely reflects the concept that data processing should be more oriented to the institution's overall management information needs, only one of which is financial.

—Many MIS control function failures have occurred in situations where attempts were made to develop all performance standards and targets before beginning a reporting system. Our recommended strategy is first to develop and obtain general agreement on the reporting framework; then begin to report resource utilization within this framework, even if accepted standards are not yet available; and then to establish and incorporate standards and targets as they are developed.

—There are no generally accepted productivity standards for some functions such as security, social service, engineering, and the like. Our recommendation is that, in such circumstances, it is imperative to adopt some measure of quality. If one then monitors simultaneously resource utilization and quality for a sufficiently long period, the manager will find that either (1) the quality measure is unresponsive to varying levels of resources, or (2) certain relationships between key inputs and outputs can be identified. In the former case, the manager needs a better or more sensitive measure of quality. In the latter he has the basis for objective assessment of the cost/benefits of changes in resource levels, which is the type of information required to establish standards of performance.

—The management information systems of today's hospital must be cost-justified. However, to attempt to do so application by application on a direct cost-replacement basis is to force a disintegrated, inefficient system. Indeed, this kind of "creeping incrementalism" misdirects and obscures the overall goals of an MIS. Cost justification must be carried out within the context for

MIS. The plan must be understood by management, periodically updated (perhaps quarterly), and presented in such a fashion that the inevitable conflicts for resources and the ensuing trade-offs of priorities are clear to management.

—In a major institution the MIS function should be guided by a steering committee with wide representation from both resource and program management. The principal activity of such a group would be the approval of the plan and its updates and the assignment of priorities. It should be clear that without a well-understood plan, relative priorities are meaningless.

Conclusion

Some medium- to large-size hospitals are now moving toward a program-resource concept or matrix format. The evolution, recognition, and formulation of the concept will require managers to adopt a systems approach for addressing the special requirements inherent in such an organization.

The basis for decision-making in planning, operations, and control is, of course, adequate and timely information. We feel that a well-developed and implemented MIS is the heart of the systems approach to management.

Newly developed techniques such as program planning and budgeting, zero-base budgeting methods, financial modeling and others must now be understood and utilized by managers if they are to succeed in their job, that is, balancing quality health care delivery with the spiraling costs of such services. It is our contention that use of these and other management science techniques will allow hospital managers to keep pace with inevitable changes.

References

1. Davis, S.: Organizing a Psychiatric Hospital on the Program-Resource Concept. Hosp Comm Psych, February 1970.
2. Neuhauser, D.: The Hospital as A Matrix Organization, Hosp Admin, Fall 1972.
3. Johnson G. V. and Tingey, S.: Matrix Organization: Blueprint of Nursing Care Organization for the '80's, Hosp Hlth Sci Admin, Winter 1976.
4. Pyhrr, P. A.: *Zero-Base Budgeting: A Practical Management Tool for Evaluating Expenses.* Wiley Press, 1973.

The Mount Sinai Journal of Medicine
Vol. 44, No. 5, September-October, 1977
Printed in U.S.A.

The City Hospital System and Affiliations with Medical Centers

RAY E. TRUSSELL, M.D., M.P.H.

The Early Sixties

The responsibilities assumed by the City of New York for more than two centuries for the health care of enormous numbers of the indigent and near indigent have resulted in a vast system of public hospitals. Yet the forces of history have been such that the ability of municipal hospitals to render care is now entirely dependent on the voluntary health care sector of our city, namely the medical schools and the voluntary teaching hospitals. It was not always so. At one time both the unaffiliated as well as the affiliated city hospitals were considered prestigious and were eagerly sought after for training and experience. However, the proliferation of specialty training programs, coupled with the failure of the city administration and the entrenched and sometimes intransigent medical staffs and boards to adapt to changing times led to a deteriorating professional situation in the unaffiliated public facilities. In the late 1950s and in the early 1960s, the concern of private individual citizens and citizen organizations led to an open assessment of what was happening to the unaffiliated public hospitals. In turn this led to corrective actions which were made possible only through the courage and wisdom of people such as Gustave Levy and his fellow trustees, and similar presidents and trustees of other medical schools and teaching hospitals. While serving as the Executive Director of Mayor Wagner's Commission on Health Services, which was appointed in 1959 with Mr. David Heyman as Chairman, the author participated in an uninhibited study of the public services rendered and the proprietary services licensed by the City. In the report of the Commission on Health Services (1960): "The main focus of attention was on the deteriorating situation in the unaffiliated municipal hospitals; problems of house staff recruitment for some; problems of loss of approval of training programs; problems of personnel, maintenance, and coordination of services for all" (1). Serious shortages of house staff were predicted as a result of the examinations given by the Educational Council for Foreign Medical Graduates (ECFMG). The Commission recommended: "Full-time directors of services; affiliations financed by the City; closing or converting to other uses certain institutions; and various other steps to improve the overall situation" (1).

Subsequently, in 1961, the author was drafted to become Commissioner of Hospitals to deal with the crisis. In reporting to the Academy of Medicine (1)

From Beth Israel Medical Center, New York, N.Y. 10003.

Requests for reprints should be sent to: Ray E. Trussell, M.D., General Director, Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, N.Y. 10003.

in the first few months of the efforts to reorganize the department, the author made certain comments which are excerpted here:

> It should be kept in mind that the discussion concerns 22 institutions with about 19,000 beds; a current operating budget of about 180 million dollars; a personnel roster, exclusive of house staff and student nurses totaling about 35,000 people; a direct service load of about 275,000 admissions; 2,600,000 clinic visits and 400,000 ambulance trips a year. The average daily home care census is about 2,100 patients. The psychiatric services at Bellevue and Kings County Hospitals admit as many patients each year as the 27 State Mental Hospitals. The Department collected through insurance, direct payments from individuals and agencies and from other sources about $52,000,000 in 1961. In addition, the Department certifies City charge patients in voluntary hospitals to the Comptroller for payment for care for the Charitable Institutions Budget. For 1960, such payments probably exceeded 40 million dollars. Such staggering figures are a sobering influence in overall community planning. Our voluntary hospital system is on the thin edge of solvency and the uncontrolled proprietary hospital building boom may push certain of these voluntary hospitals into bankruptcy and force governmental assumption of more responsibility through direct service or more subsidy. It is just because of such considerations that the Hospital Council has made its recent recommendations about the various ways in which municipal and voluntary hospitals can and should work together for reinforcement and better service to the community.
>
> In January 1961, some of the Commission on Health Services predictions came true in a most dramatic way. As a result of failing the ECFMG examination, a substantial number of house staff physicians at the Harlem Hospital were restricted to non-patient care activities. This action came at a time when, due to weather conditions, a high accident rate prevailed in a community which normally makes extensive use of emergency room services. The result was an acute manpower crisis and an extremely distressful patient care situation developed. Let us hope that there will never be another. In a city as rich in resources as New York, injured people should not have to sit on benches for lack of stretchers; should not have fractures left unset for five days for lack of physicians; should not lie on stretchers on the floor for lack of beds—yet all this and much more occurred in those painful days a year ago, largely due to insufficient physicians and technicians.
>
> The number one problem, of course, was an adequate supply of physicians in the unaffiliated hospitals. Seven of the municipal hospitals are manned by universities and the public is fortunate that this is so. This group, on an overall basis, has relatively few medical manpower problems. The remaining 15 hospitals have been experiencing varying degrees of difficulty in maintaining adequate numbers of attending staff and/or house staff. New York, which was once the largest center on which young physicians converged from all over the world for training in both municipal and voluntary hospitals, now must compete against a national network of approved graduate training centers in the face of a relative shortage of national and foreign graduates to fill the available openings. Not a single American-trained intern has been recruited by an unaffiliated municipal hospital through the matching plan for several years. (See Table I.)
>
> New York City's problems have been compounded by the large number of institutions it operates. No other city has gone so far in making municipal hospitals so available so close to local communities. It is paradoxical, in the face of so much effort to provide service, that the forces of history were eroding standards of care. At any rate, it is quite clear that New York City should not build any more unaffiliated municipal hospitals, and that the present system needs reorganization in the interest of improved patient care.
>
> An approach to reducing house staff requirements has been to close or change the functions of certain hospitals. The Gouverneur Hospital on the lower East Side of Manhattan was the first to close its in-patient service. An obsolescent plant, loss of affiliation, loss of residency approvals and loss of accreditation, together with staffing problems raised serious questions as to the wisdom of maintaining the in-patient services. After intensive study by a panel of consultants and a decision by the Medical Board not to go on, the in-patient services were

TABLE I

Distribution of Intern and Resident Positions Affiliated and Nonaffiliated Hospitals October 1963

	Medical School Affiliated General Hospitals			Non-affiliated General Hospitals			
	Bellevue	Bronx Municipal	Kings County	City Hospital Center at Elmhurst	Coney Island	Fordham	Queens Hospital Center
Available Intern Positions	*108*	*49*	*136*	*27*	*25*	*13*	*28*
Filled by American or Canadian Graduates	98	49	125	0	0	0	0
Filled by Foreign Graduates	1	0	5	16	23	13	28
Vacancies	9	0	6	11	2	0	0
Available Resident Positions	*295*	*219*	*274*	*103*	*58*	*48*	*92*
Filled by American or Canadian Graduates	207	162	147	7	1	0	13
Filled by Foreign Graduates	70	56	95	77	49	35	70
Vacancies	18	1	32	19	8	13	19

closed. However, the clinics, emergency room, home care and ambulance services are essential in the area because of its cultural and economic characteristics. The Department and the writer are deeply grateful to the Beth Israel Hospital for assuming the responsibility for these services on a contractual basis for a three-year period.

A very rewarding approach to improving certain municipal hospitals has been through new affiliations or associations with strong teaching voluntary hospitals or universities. This route assures those municipal hospitals fortunate enough to have such assistance of either complete staffing at all levels, or of individual departmental staffing, or of rebuilding for the future as a training center.

More recently, Mount Sinai Hospital agreed to accept responsibility for the staffing of Greenpoint Hospital. This outstanding service to the community comes at a time when the hospital's plight is desperate. There are no interns and no medical or pediatric residents. The facility is only partially opened, yet it is a completely renovated building situated in a community with great need for municipal hospital service. The first five directors or assistant directors were nominated by Mount Sinai and confirmed by the Dean's Committee within the past three weeks. Additional attending and house staff are being recruited and the hospital should be fully in use by July 1st.

These contracts did nothing more than to put the unaffiliated city hospital on the same footing with the previously affiliated city hospital, but at city expense instead of university expense. Administratively, the relationships were identical; all were subject to the policies of the Commissioner of Hospitals, the rules and regulations of the department. All were administered by city administrators who were accountable to the Commissioner. But the professional staffing was a service purchased by the city from the voluntary system. This was necessary because the job was not getting done under the combination of city civil service and the voluntary attending doctor system.

The Department, the Board of Hospitals, and I were grossly misinterpreted at times as to our intent with these contracts. Our effort has been to redistribute the medical manpower and the technical manpower around the city, which was concentrated in the large teaching centers, both voluntary and municipal. There was, for example, a terrible shortage of good patient care in Harlem Hospital, yet it was surrounded by Presbyterian, St. Luke's, Mount Sinai. This required organization and financing to overcome.

In a subsequent report to the Academy (2) the author concluded his presentation with the following comment: "I shall close by pointing out that in New York City, government has turned to all that is good in the voluntary systems to discharge the public responsibility. This series of combinations of voluntary resources, governmental responsibility and authority, and channeling of public funds offers some lessons that can well be studied."

In Retrospect

Looking back 15 years, much satisfaction can be gained by the affiliates for their part in saving the city hospital system from total collapse. A massive redistribution of health manpower was achieved. By now some have moved on to the status of Commissioner or Departmental Chairman. More personnel were available; more and different kinds of services were developed. Facilities and equipment were upgraded. Although affiliate performance was unequal, in general a better pattern of house staff recruitment occurred through the upgrading of the training programs in the previously unaffiliated institutions. As a result, our foreign guests received better training and American-trained interns and residents again began to work in the previously unaffiliated institutions. This was most obvious in totally integrated programs such as Montefiore-Morrisania and later in Beth Israel-Gouverneur.

Perhaps the greatest achievement was to provide some budgetary flexibility through the device of lump sum contracts which made it possible to remain competitive in the marketplace and to deal with emergencies.

At the time of the expanding affiliation program in the early 1960s, there was a sense of pioneering, a real working partnership between the public and voluntary sector and great pride in what was being accomplished. However, on July 1, 1966, Medicaid and Medicare became effective. The census began to drop in public hospitals and the affiliations began to suffer a series of stresses and strains which have had their negative influence. A reporter for a now nonexistent newspaper wrote what he considered to be an exposé charging the voluntary hospital sector with misuse of funds. Both a senator and comptroller with political ambitions took up the attack on the affiliates and sought every possible way to embarrass them. A blue ribbon panel was appointed by the Governor to investigate the allegations; the State Investigations Commission issued a report; the City Commissioner of Investigations wrote a report. All the negative statements were duly publicized. The fact that some of the reports gave the affiliates a clean bill of health and commended their role in upgrading and preserving health care in New York City was duly ignored.

If one examines the various criticisms leveled at the affiliates, the deficiencies which were reported clearly lent themselves to routine administrative correction which did not always occur. The new affiliation program was one which needed time to develop clearcut policies and an accepted tradition which it deserved. Unfortunately a series of further events occurred which made it even more difficult for the affiliates to perform to their satisfaction in the public hospitals.

The most devastating blow to the affiliation was the "rollback" imposed by the president of the municipal union with the most dominant voice in the public hospitals as a condition of not blocking the pending legislation which was intended to create the new Health and Hospitals Corporation. This rollback resulted in very large numbers of excellent affiliate personnel being placed on the municipal payroll with no foreseeable future as they saw the situation. As a result, an enormous erosion of competent manpower occurred which severely limited the ability of physicians in the City hospitals to perform as well as before. Further improvement of services became impossible.

The Health and Hospitals Corporation, which was supposed to be the answer to all problems in public hospitals in New York City, was politicized by the legislative events which surrounded its creation. Its track record to date has been anything but commendable.

In more recent years the intrusion of community advisory boards into professional and administrative affairs at the City hospitals has created further problems. In some hospitals, community boards interfere with program development, with operations, and actually control the appointment of administrators who are, in theory, accountable to the President of the Health and Hospitals Corporation. In at least one hospital they controlled the appointment of Department Heads—an area in which they had neither expertise nor experience. Such confusion and mis-assignment of responsibilities are extraordinarily counterproductive.

The additional problems created by inflation and the tightening money situation in New York City and State have resulted in severe cutbacks in personnel and programs, and reduced ability to render service.

The attitude of key staff in the Health and Hospitals Corporation towards the affiliates and the consequent reactions have resulted in an adversary relationship instead of leadership and cooperation. An alienation has developed which is destructive and offers little hope for the future in City hospitals unless reality is faced by the City and the Corporation. At the present time, affiliate personnel are disgusted, demoralized and have a grim view of the future. They feel unappreciated for what they have accomplished in caring for the poor and for staying and working under the most difficult circumstances. If the City of New York does not recognize the danger signals, further erosion of health care is inevitable.

The destruction of the Beth Israel-Gouverneur Hospital affiliation is a case in point. Termination by the Health and Hospitals Corporation of this affiliation has been followed by the near-collapse of Gouverneur as a viable health care entity in the Lower East Side. Personnel are now entirely on the City payroll, which is the beginning of the end because future staff will no longer be recruited on the basis of the best in the marketplace, but rather what the least amount of money can retain.

The irony of the situation is heightened by the fact that in the public sector proportionately there has been more replacement of capital facilities than in the private sector. For the City of New York to maintain a system which to a very large extent, consists of entirely new facilities, and at the same time to be in a situation where it is unable to provide the resources for the medical staff to function properly, is deplorable.

With National Health Insurance due in the foreseeable future, and with the existing excessive beds already in the City hospitals due to the patients' free choice with Medicare and Medicaid, it is clear that there will be more excess beds in the public facilities. The system will have to shrink. But those public hospitals which must stay open—perhaps for decades to come—deserve adequate financing, public encouragement and a restoration of professionalism in a central office dedicated to excellence. The City must recognize that it is now more than ever dependent on the voluntary sector, but that the voluntary sector has become, understandably, totally distrustful of the City. The enormous pool of volunteer talent in the health sector available to local government is alienated and far less available than it was in the past. New York City cannot afford this loss of interest by voluntary leaders. New York City is dependent on the voluntary sector for operation of its public care institutions, and if the City wants to have its needed public hospitals truly survive, and capable of providing quality health care to the poor, it will have to reach out for the help which it has rebuffed in recent years.

The citizens of New York owe much to the trustees, to the administrators, and to the medical staffs from the voluntary sector who have worked so long and so hard to provide decent health care to the poor, and who can be justly proud of what they have done.

References

1. Trussell, R. E.: The Municipal Hospital System in Transition, Bull NY Acad Med 38:221–236, 1962.
2. Trussell, R. E.: Current Efforts in the Municipal Hospitals, Bull NY Acad Med 43:211–218, 1967.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 5, September-October, 1977
Printed in U.S.A.

Primary Care and Community Medicine

KURT W. DEUSCHLE, M.D. AND SAMUEL J. BOSCH, M.D.

In the decade of the 1960s the nation's health policies fostered the establishment of programs and projects in "community medicine." During the last five years United States national health policy as expressed through federal support for medical care and medical education has strongly advocated programs and projects in what now popularly has been labeled "primary care." These national health policies would appear to be speaking to major problems and needs that belong to the health care system as a whole. Because community medicine and primary care are different components of a health system with apparent overlaps and areas of common interest they need to be defined better, they require further review and deserve careful analysis. The purpose of this paper is to analyze some of the issues and differences involved in this apparent overlap, to discuss how the medical schools in the United States have responded in general to these issues, and to present the approach to these problems that has evolved at Mount Sinai School of Medicine of The City University of New York.

Before analyzing the health care issues which primary care and community medicine are alleged to address and how they interrelate, it is essential that working definition of these terms, as different forms of service, be established at the outset.

The traditional and well-recognized service role of primary care physicians is in the provision of health services to individuals, and the routine of their practice involves the identification of health problems (diagnosis) and the attempt to solve these problems (treatment) at the primary level of medical care. Many definitions for primary care can be found in the literature. First of all, there seems to be wide agreement that primary medicine is within the personal health system and therefore is focused on the health needs of individuals and families (1). Primary medicine is first-contact medicine, it assumes longitudinal responsibility for the patient regardless of the presence or absence of disease and serves as the "integrationist" for the patient (2). Thus, it is the function of general medical care to: (a) provide ready access to solutions for ordinary problems; (b) identify, from innocent-appearing situations, those few that are potentially serious, and to provide properly for them; and (c) provide appropriate science-based Samaritanism (3).

Many types of health professionals are now claiming and insisting that they are individuals who provide primary care. These include the traditional but vanishing general practitioners, the recently established family medicine

From the Department of Community Medicine, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Kurt W. Deuschle, M.D., Department of Community Medicine, Mount Sinai School of Medicine, Fifth Avenue and 100 Street, New York, N. Y. 10029.

specialists, general internists, general pediatricians, obstetrician/gynecologists, and psychiatrists. The innovative physician-extender providers such as the various nurse clinicians and physician assistants are also claiming the right to be considered primary care professionals. On the other hand, health professionals who organize themselves in groups are claiming that they are primary care providers as a group and that in such manner they are meeting the demand for general health services.

Prodded by state legislation and federal appropriations, academic medical centers have responded by establishing family medicine and primary care training programs. A survey by the Association of American Medical Colleges in 1974 indicated that approximately one half of all medical centers had developed programs for graduate training in family medicine and another 25 percent intended to do so (4). Parenthetically it should be noted that the Mount Sinai Medical Center and its hospital affiliates do not yet have a primary care or family medicine residency track.

In simple terms community medicine can be defined as the academic discipline that addresses the identification and solution of health problems in population groups (5). The germinal core of community medicine continues to be the basic disciplines of epidemiology, biostatistics, and behavioral and management sciences.

Community Medicine was established as a reformulation of modern public health and preventive medicine at the University of Kentucky Medical Center with a reorientation from a strictly public official agency kind of practice to a clinically related situation at the community level (6). This reformulation was reinforced by the community medicine departmental designation. In Kentucky the Dean was supportive of the introduction of the third faculty concept (7). That is, in addition to the basic science and clinical faculties, a third faculty group with knowledge and skills in problem solving in community health was essential in order to build a comprehensive approach to health services in the community. The restructuring of traditional public health and preventive medicine departments which often were still committed to classic studies of infectious and chronic diseases gradually shifted to concern for health care delivery problems.

The community medicine movement of the 1960s can be summarized as the redefinition of modern public health focusing on problems of health care delivery and environmental health which were becoming highly visible in United States society. The less traditional and still not well-recognized service role of community medicine physicians is in planning, development and evaluation of health services for populations; and the routine of their practice involves the identification of problems (epidemiology) and the attempt to solve these problems through better organization of health services at all three levels of care—primary, secondary, and tertiary (8).

Health care studies around the country in general have demonstrated that the extensive gap between community expectations concerning health services and what the public receives is perceived by the public as a lack of general practitioners or family doctors. This perception voiced as a problem of high priority has become a political issue. For example, between 1965 and

1971 more than $400 million dollars of federal financial assistance have been provided for planning and implementing ambulatory care programs in low income communities and about 100 neighborhood health centers sprang up as a response to that need (9). Academic departments of community medicine were frequently designated as the organization responsible for linking and operating these neighborhood health centers from the university base. There is a mixed history of success which surrounds academia's experience with neighborhood health centers but suffice it to say here that health policy makers and the public usually associated and sometimes confused these primary care centers (medicine in the community) with community medicine. The linkages of community medicine to the "provision of urban and rural health services to the poor" issue as well as general issues of inequity of services for the disadvantaged black and Hispanic groups, distracted some of the academic leaders in community medicine and motivated them to concentrate on health problems as they related to civil rights and political activities in society.

Within the university medical centers themselves, confusion and often serious conflict has arisen around the departmental status of primary care, family medicine and community medicine. One approach which has been developed is to incorporate family medicine into community medicine. However, conflicts arise here with respect to responsibility and accountability for the core components of the clinical input for internal medicine, pediatrics, psychiatry, obstetrics/gynecology and other subspecialty areas. Moreover academics of family medicine are not overly enthusiastic about sharing their opportunity to establish a beachhead for their specialty in terms of a full-time academic department of family medicine. The critics of the purist family medicine department approach point out the lack of a research tradition or capability in the family medicine field. The epidemiologic, behavioral, and managerial sciences which are most relevant to the pattern of research needs in primary health services are found in departments of community medicine.

Academic "turf" conflicts are not infrequent in academic centers. Although the marriage of family medicine and community medicine is sometimes quite synergistic, splits have occurred with two independent departments emerging. In some instances community medicine departments have actually been dissolved in favor of a Department of Family Medicine or Primary Care. The family medicine and community medicine relationship is still fragile and it is, perhaps, too early to predict the predominant academic pattern which will be followed in the 1980s.

The picture at Mount Sinai may be somewhat atypical with respect to primary care and community medicine, but they have been clearly separated in this institution. Mount Sinai's commitment to community medicine has been its major formal academic thrust as enunciated in the Popper concept (10). Family medicine as a specialty is not being offered as an area of training.

On the other hand, a lukewarm interest in primary care has been developing and a Committee on Primary Care was established as part of the Dean's Excellence Committee. That committee has established that a primary care program is more suitable than a family practice for the urban setting. The committee has, in addition, advocated that educational role models for primary care programs be provided by the general internist and the general pediatrician (11).

From the outset, the founders of the medical school reasoned that a social commitment would be meaningless if it could not be translated into a full-time faculty of community health scientists working side-by-side on a daily basis with the basic scientists and clinical faculty of the medical center. They therefore established a generously endowed Department of Community Medicine, envisioning it as an essential resource for contemporary medical education, research, and service. Today the Department of Community Medicine is organized as a large, interdisciplinary "third faculty" of the medical school that complements the basic and clinical sciences faculties. One of the Department's principal mandates is to serve as a bridge between the resources of the medical center and those of the surrounding community, East Harlem, in a joint problem-solving effort. The overall service goal in East Harlem is to contribute to the improvement of health care services in the area *without* assuming direct responsibility for the administration and/or actual provision of health care services and taking into consideration the pluralistic nature of our society. In order to meet that goal the Department *participates with* a broad variety of East Harlem community groups (consumers and providers) in a continuing process of identifying and solving problems related to health. In partnership with these groups the Department encourages a more rational utilization of existing resources in the area, fosters interorganizational linkages, mergers and agreements, and has as an ultimate goal the achievement of logical regionalization of health services in the area, taking into consideration that resources are inevitably limited.

The five basic activities that define community medicine practice at Mount Sinai can be summarized as (a) assisting community groups (providers and consumers) in the translation of recognized health needs into the formulation of specific problems, (b) participating with the community groups in the identification of possible alternative solutions to their problems, and in reviewing and resetting the priorities of alternative solutions in terms of their feasibility, (c) aiding the community groups in developing program goals and objectives and in converting them into action programs, (d) assisting hospitals and other providers in the region to define their roles in relation to consumer needs, and to cooperate with them in the development of new organizational models, and (e) communicating experiences and results derived from the implementation of the above mentioned aims among the different consumer and provider groups in the region and contributing to an effective coordination of their resources and efforts.

The specific programs and projects in the public and private sector that are a result of these activities have been discussed elsewhere (8). The significant advances made through these activities in fulfillment of the Department's service goals can be described through three representative examples in which intra- and interorganizational changes are taking place and are facilitating an active move toward the regionalization of health services in the area.

Example 1

At the request of the Department of Health of the City of New York, and in collaboration with the Model Cities program, the Department engaged in 1971 in the planning and development of a demonstration project that transformed a New York City wellbaby clinic (the Wagner Health Station) into a model child care program, controlled by nurse practitioners, and offering primary care as well as outreach preventive services in a geographically defined area. The project served an estimated total population of 1800 preschool children who lived in Health Area 17. In two years registration grew to approximately 1350 children, compared to 800 before the start of the project (12). On July 1, 1975, the administration of this same program was successfully taken over by the East Harlem Tenants Council, a community organization, and became the nucleus of an East Harlem community-governed neighborhood health center for the total care of families in the area. Basic components of the model such as health teams led by public health nurse practitioners, medical care protocols and outreach activities, have been maintained and expanded by the new administration. With the continuing technical assistance of the Department, the program has been designed in such a way that it eventually can be converted into the group practice of any health maintenance organization (HMO) in the area (8). This neighborhood health center now offers comprehensive primary health care and related services to families of a specific target population from East Harlem and is linked to the Hospital for Joint Diseases and the Mount Sinai Hospital for the specialty and subspecialty ambulatory and inpatient care of the people registered at the Center. The projected goal for full operation is to serve 24,000 to 30,000 registered patients and the projected ultimate location of the program is the "Taino Towers," a low-income residential and human services complex at Third Avenue and 123rd Street.

Example 2

At the request of the Hospital for Joint Diseases, a voluntary hospital located in the northern part of East Harlem, the Department functions in a planning capacity and is involved with the staff of that hospital in the process of reexamination of the goals and objectives of the institution as it moves toward a new identity as a community hospital. Since the hospital is affiliated with Mount Sinai, the Department is an active consultant in the process of redefining the role of this hospital within the evolving health care delivery system of the community.

Example 3

At the request of Mount Sinai Hospital itself the Department of Community Medicine has functioned and continues to function as a research and technical assistance unit for the improvement of ambulatory care services in the hospital. A team of three social scientists is continuously engaged in a program of concurrent evaluation, a type of action or "policy" research designed to study health care delivery and to provide a regular flow of information for modifying patient services. The field of study covers interpersonal and interorganizational relations among staff, and between staff and patients, that affect patient care. Specific topics of study up to now have been unmet patient demands, improvement of existing services, the effect of cultural differences between consumers and providers on compliance with health care, and responses by consumers to a joint provider-consumer poll of satisfactions and dissatisfactions with the outpatient services.

As a result of such activities , a community-based regionalized system for personal health services is emerging in the area "from the bottom up" and it is a system that is viable in a pluralistic society such as ours (4).

At this point in the history of Mount Sinai School of Medicine an increasing number of opportunities have grown out of this form of community medicine, engaging our faculty in cooperative projects with our clinical colleagues in the hospital and in the school. A variety of joint programs are in progress with the Departments of Medicine, Pediatrics, Obstetrics, Surgery, Psychiatry, and Dentistry—built around health care delivery issues and categorical problem areas such as the early detection of impairments and diseases. Without the integrated clinical sciences, basic sciences, and community medicine interplay on a day-to-day basis and without a participatory approach to health care, we doubt that so many and diverse opportunities for joint actions would have evolved.

References

1. White, K. L.: Primary Medical Care for Families, New Engl J Med 277:847, 1967.
2. Alpert, J. J. and Charney, E.: *The Education of Physicians for Primary Care*. U. S. Department of Health, Education, and Welfare, Public Health Service, DHEW Pub. No. HRA 74-3113. Autumn 1973.
3. McDermott, W.: General Medical Care Identification and Analysis of Alternative Approaches. Bull Hopkins Hosp 135:292, 1974.
4. Schroeder, S., Werner, S. M., and Diemme, T. E.: Primary Medical Care in the Academic Medical Centers: A Report of a Survey by the AAMC, J Med Educ 49:823–833, 1974.
5. Deuschle, K. W. and Eberson, F.: Community Medicine Come of Age, J Med Educ 43:1229–1237, 1968.
6. Willard, W. R., et al.: Philosophy of Medical Education at the University of Kentucky, 1956, Mimeographed report.
7. Deuschle, K. W. and Fulmer, H. S.: Community Medicine: A "New" Department at the University of Kentucky College of Medicine, J Med Educ 37:434–445, 1962.
8. Bosch, S. J. and Deuschle, K. W.: The Role of a Medical School in the Organization of Health Care Services. Proceedings of the Fifth Annual Symposium on Medical Education, Bull NY Acad Med 53:449–464, 1977.
9. Zwick, D. I.: Some Accomplishments and Findings of Neighborhood Health Centers, Milbank Mem Fund Quart 50:387, 1972.
10. Popper, H.: The Mount Sinai Concept, Clin Res 13:500–504, 1965.
11. Anderson, P. J. and Stapleton, C. J.: Summary of Recommendations from the Task Force of the Clinical Excellence Committee, September 1976.
12. Thomstad, B., Cunningham, N., Kaplan, B.: The Doctor-Nurse Game: Changing the Ground Rules, Nursing Outlook 23:422–427, 1975.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 5, September-October, 1977
Printed in U.S.A.

Perspectives in Preclinical Management of Cancer: Initiation of a Mesothelioma Therapy Research Program*

IRVING J. SELIKOFF, M.D.

In our hospital's corridors, a colleague will often stop to ask, only half in jest, "Well, what's the carcinogen of the week?" The rejoinder suggests that the question almost answers itself: "Is it better to know the causes of cancer, or not to know them?"

We have now entered an extraordinary new phase in our approach to cancer. For the first time in human history, we are learning the causes of the disease. We now have the opportunity to control those causes, to prevent problems in the future and to help those already exposed and at high risk of developing neoplasms.

We have come to understand the long period of clinical latency between onset of exposure to carcinogenic agents and the subsequent appearance of tumors. Youngsters begin working with vinyl chloride at 18; their liver angiosarcomas are seen at 40. Hiroshima leukemias peaked six or seven years after 1945; vaginal adenocarcinomas strike young women in their late teens, although exposure to diethylstilbestrol occurred only in utero. The long incubation period of cancer has again and again tricked and confused us, obscuring evidence of etiologic relationships. The bland immediate effects of thymus radiation in the 1940s gave no hint of the thyroid neoplasms to be seen in the 1960s and 1970s. Rubber companies did not know that benzidine or beta naphthalamine would cause bladder tumors in their workers 20 or more years later, nor did we predict in the 1920s–40s what the dramatic increase in cigarette smoking would bring in the 1950s–70s.

The same delays between cause and effect that misled us may also now be turned to our advantage, for as we identify agents that can cause cancer, we also identify those people who were exposed to them during the years of our quiet ignorance and inattention—people who are at predictably high risk of developing disease. We know, at least statistically in groups, who has a considerable chance of having cancer.

From the Department of Community Medicine, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

* Presented at the American Cancer Society's Science Writers Conference, Sarasota, Florida, April 4, 1977. From the Environmental Cancer Research Project of the American Society and the Environmental Sciences Laboratory, Mount Sinai School of Medicine of The City University of New York.

Requests for reprints should be sent to: Irving J. Selikoff, M.D., Department of Community Medicine, Environmental Sciences Division, Mount Sinai School of Medicine, Fifth Avenue and 100 Street, New York, N.Y. 10029.

TABLE I

Expected and Observed Deaths among 17,800 Asbestos Insulation Workers in the United States and Canada January 1, 1967–January 1, 1975

	Deaths	
	Expected*	Observed
Total deaths all causes	1483.38	2003
Cancer, all sites	281.49	867
Lung cancer	92.28	427
Pleural mesothelioma	**	52
Peritoneal mesothelioma	**	92
Cancer of esophagus	5.77	16
Cancer of stomach	12.71	22
Cancer of colon-rectum	33.87	53
Cancer of larynx	4.45	9
Cancer of oro-pharynx	7.41	17
All other cancers	125.00	179
Asbestosis	**	141
All other causes	1201.89	995

* Expected deaths based upon white male age-specific mortality data of the U.S. National Center for Health Statistics for 1967–1974 and extrapolated for 1975.

** These are rare causes of death in the general population. On January 1, 1967, there were 17,800 men on the rolls of the International Association of Heat and Frost Insulators and Asbestos Workers in the United States and Canada. With the cooperation of the Union and its members, each has been followed since. This table, based on statistical analyses of the Department of Epidemiology and Statistics of the American Cancer Society, summarizes the mortality experiences of the Union's members for the nine years to January 1, 1976. We are grateful for the generous assistance of Mr. H. Seidman, Chief Statistical Analyst of the Department, for this analysis, and to Mrs. J. S. Kaffenburgh and Mrs. F. Perez for their capable and conscientious efforts in tracing and recording the detailed progress of the group.

Can we do something about this? Must we wait until neoplasms appear? Or is it possible to find methods of much earlier diagnosis, and much more effective treatment? We are faced with just such a dilemma concerning mesothelioma and asbestos. From 1930 to perhaps 1970, very inadequate precautions were taken in the use of this ubiquitous material, in mines, mills, factories, shipyards, the construction industry; in the manufacture and use of several thousand articles. The Public Health Service has calculated that there are approximately 1,000,000 men and women who are either currently employed or who were formerly employed as "asbestos workers." Data suggest that from 5 to 7 percent may develop mesothelioma, an invariably fatal neoplasm of the lining of the chest or the lining of the abdomen. (In addition, 3 times as many will die of lung cancer). This unhappy projection does not include people who were not "asbestos workers" but were nonetheless significantly exposed to the mineral in shipyards, construction sites or elsewhere, or in households contaminated by the fibers brought home on the clothes, shoes, or hair of the breadwinner decades before. What proportion of these additional millions of Americans will die of mesothelioma is not yet known.

The impact of this problem perhaps can be appreciated by considering what is now happening in one small union, the Insulation Workers*, in the building trades (Table I). Although it has but 18,000 members, hardly a fortnight goes by without a death of mesothelioma, two-thirds before the age of 65. Average duration of life from time of diagnosis is less than a year.

The next thirty years will be difficult ones, as the mistakes of the past thirty catch up with us. Is this inevitable? Must we look to 2,000 or more deaths each year of mesothelioma, well into the next century? Perhaps—but one hopes not. The concept is developing that intervention in the course of mesothelioma in its prodromal stage may be possible. It is this perspective that underlies the initiation of the Mesothelioma Therapy Research Program**—that research be undertaken to find techniques for very early, preclinical diagnosis to make feasible much earlier, preclinical treatment. We will be able to evaluate the new methods among the asbestos-exposed individuals now under surveillance; the usefulness of the procedures will be measured by the prevention of disease and the efficacy of treatment. It may even be anticipated that the lessons to be learned and the discoveries to be made will have relevance to the broader problem of management and treatment of environmentally induced cancers to blunt the otherwise apparently inexorable progression of environmentally induced cancer.

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* International Association of Heat and Frost Insulators and Asbestos Workers, AFL-CIO/CLC.

** On January 7, 1977, the Mesothelioma Therapy Research Program was initiated at the Mount Sinai Medical Center, under the direction of Dr. James F. Holland and Dr. Irving J. Selikoff, as a joint effort of the Department of Oncolory and the Environmental Sciences Laboratory of the Department of Community Medicine. Its purpose is to develop improved methods of management for pleural and peritoneal mesothelioma. Initial support for the research has been generously provided by both the Union (International Association of Heat and Frost Insulators and Asbestos Workers) and the Johns-Manville Corporation.

The Mount Sinai Journal of Medicine
Vol. 44, No. 5, September-October, 1977
Printed in U.S.A.

Experimentation and Ethics*

SHERMAN KUPFER, M.D.

Philosophers have been debating ethical issues as they relate to medicine and clinical investigation in one form or another in relative quietude for centuries. Why now the growing interest in ethics in biomedical sciences and health care delivery? Why is widespread anxiety and apprehension more apparent than ever before? I submit three reasons for consideration:

1. Publicity given to the behavior of so called scientists during the Nazi holocaust as well as to the practices of some others about whom questions have been expressed in respect to the ethics of their science. Interestingly enough, the agencies of the government have been guilty of the most callous disregard of basis guidelines in respect to research involving human subjects. Witness the recent disclosures regarding research with mind-altering drugs, nerve gas, and bacteria. It is not surprising, therefore, that society feels pressured to protect itself from such irresponsible and unethical actions. The paradox is, of course, that the proposed laws may result in greater harm by restricting the creative and innovative capabilities of responsible thinkers and doers without imposing any legal requirement for ethical behavior on the part of some agencies of this and other governments.
2. Increasing growth of cynicism, a loss in personal and public trust and emphasis on self-centered personal goals and pleasures to the detriment of the concept of service and the legitimate aspirations and attainable expectations of society.
3. Difficulties in interpreting for the public, in an understandable way, the sophisticated technical aspects of biomedical research. In large measure, the media have been rather ambivalent in this respect. In some instances the issues have been incorrectly reported and then either not retracted or inadequately retracted. This is especially the case when the issues lend themselves to sensationalization. Rather than being informative, some reports mislead the public and create anxiety, augment fear and promote superstition. In other instances such reports lead to unfulfilled expectations and anguished frustration. On the other hand, there is a sizeable and growing cadre of reporters that has the capacity to illustrate, to clarify and to interpret scientific nuances for the benefit of a wider public ordinarily not reached by scientists, including other scientists. I hasten to add that what I have to say is not to be interpreted that a mountain has been made of a molehill, but rather that every effort be made to maintain an appropriate perspective.

From the Clinical Research Center, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

* Supported in part by NIH grant RR71, Division of Research Resources, General Clinical Research Centers Branch

Requests for reprints should be sent to: Sherman Kupfer, M.D., Director of the Clinical Research Center, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

The ancient rabbis remind us that the greatest virtue is to have good heart. The Talmud admonishes, "Begin nothing until we consider how it is to be finished, and not to be too positive in our assertions, for we are capable of error."

It is unfortunate, but nonetheless true, that a great deal of recent concern regarding rights and welfare of patients has been generated in relation to administrative practices and procedures which have little or no connection with research, such as abortion, contraception, sterilization, euthanasia, and the distribution of medical resources. I would like to point out that to my knowledge there have been few or no malpractice lawsuits filed against researchers. I would submit that this is an enviable record which the medical profession in general should be desirous of emulating in respect to routine diagnosis and treatment.

I am not going to discuss moral questions relating to abortion, contraception, artificial insemination, euthanasia, or the distribution and availability of scarce and/or expensive medical therapies. An interesting byproduct is the question of the responsibility each individual has to refrain from practices which are known to increase the risk of illnesses which utilize societal resources. These topics are all worthy of discussion in a forum directed solely at the ethics of medical practice and health care delivery rather than experimentation.

I think it would be helpful to start with some definitions. Ethics concerns itself with the identification of moral standards and the type of reasoning about moral standards which appears to be most reasonable and justifiable. This is not to say that ethics are limited to a set of moral rules. Bishop John Robinson (1) suggested that there are right and wrong aspects of actions which are recognized as such over time and across cultures. Leake (2) has stated that it is wise to distinguish between "morals" and "ethics" and suggests that "morals have to do with individual behavior and ways of conduct of individuals people as they go about their daily affairs, subject ever to their drives and whims. Ethics are the intellectual generalizations educed from an attempted analysis and formulation of individual moral actions." Simply stated there are two kinds of normative ethical systems that are most widely discussed at this time:

1. Utilitarianism—espoused by Plato and extended by the British philosophers Jeremy Bentham and John Stuart Mill
2. Formalism—originally championed by the German philosopher, Immanuel Kant.

It is a popular pasttime of the modern philosophers and ethicists to debate and contrast the basis of each of these ethical systems. How do these two ethical systems relate to science, especially to the various branches of biology and then to clinical investigation. The search for truth, the raison d'etre of the scientific method, the basis of experimental design certainly has qualities of virtue, of goodness and can result in great pleasure. Kant posited that there is one fundamental categorical imperative from which all specific moral duties can be derived, to wit: "Act only according to that maxim which you can will to be universal law." Stent (3) states that "any such all inclusive generalization would place too severe a limitation on the creative aspect of morality and limit the variety of social situations under which rational value judgments can be produced. Thus, it is clear that there are few if any moral rules which we would want to be followed without exception. As scientists, clinical investigators, and physicians, we are faced with moral dilemmas and paradoxes." I am not sure that I like Stent's choice of words when he states that ". . . we can only continue to muddle along as best we can with our paradoxical endowment." I think that it is likely that some virtue derives from the diverse principles which govern man's behavior if not his nature. In the process of agreeing to disagree, the philosophers must focus on clarifying the issues, if not their solutions.

The recommendations of the World Medical Association, adopted at the 18th World Medical Assembly at Helsinki in 1964 and modified at the 29th assembly in Tokyo in 1975 outline principles, standards, and procedures to guide medical doctors in biomedical research involving human subjects. Interestingly enough, reference is made to the conduct of research which may affect the environment and the necessity to respect the welfare of animals used for research. Reference to the environment carries special significance in these days of concern regarding recombinant DNA research.

There is much controversy and concern regarding the use of animals in research, not only in relation to general conditions in respect to their welfare, but also to the interpretation of the results of such studies. In respect to this latter point I need only call attention to the recent outcry surrounding FDA reliance on Canadian studies which reported the proclivity of large doses of saccharin to induce bladder cancer in rats. This is not the forum to debate the validity of the observations, or the interpretation of the results, but rather the measures to which we must resort to better assure the welfare of the human condition. Whose ox is being gored? Let me hasten to add that there is little or no debate worthy of attention regarding the necessity of using animals. What are the available alternatives (if indeed there are such alternatives)—their costs and their benefits?

The concern for the environment and the controversy surrounding the impact of humanity on this precious commodity is a serious matter. Nobody will deny the benefits which science has made possible, and yet the catalogue of the consequent costs is voluminous. There are some who claim that academe is too permissive an environment to expect much concern for the social and moral issues of research. On the other hand, will repressive and/or prohibiting regulation of scientific inquiry redress or minimize the ethical and moral lapses of a society in relentless pursuit of relevance and immediate application? I think not. I call to mind the brilliant studies on the structure of the atom and nuclear energy, and now we are on the threshold, if not one step beyond, in respect to recombinant DNA research. It is interesting to note, and the record will substantiate, that scientists themselves called for a moratorium on such research at the Asilomar conference. This action led to the development of guidelines for the conduct of future research and increased the level of consciousness of biohazards extant. I submit that irrespective of the supposed virtues of national, state, or local legislation, one versus the other, or all three versus the moral intent of the guidelines, the real issue is to decide what measures will effect the greatest likelihood of compliance including, most importantly, the resources which society is willing to make available. I do not think it likely that there will ever be complete agreement on the morality of the issue, or total and uniform compliance by scientists everywhere, especially as technologies change, to assure that such research can be prevented by legislative fiat which might even include the death penalty or long imprisonment. History does not suggest that such an approach offers much certainty of success. Accordingly I think that society must come to grips with the responsibility of providing the manpower and mindpower to assess the risk/benefit ratio of this research and technology, as well as the physical facilities to assure that the probability of error and/or accident does not exceed the accepted limit. One thing else, also, to assure that compensation will be available for injury irrespective of fault, if indeed there be fault.

Perhaps I have wandered a bit from the World Medical Association recommendations, but I do think that these developments were foreseen by the philosophers. Notwithstanding this glimpse into the future, the major thrust of their recommendations, as stated in many earlier codes (4) which governed the behavior of physicians, is the reminder that the patient's health is the physician's first consideration. The physician also is charged to safeguard the health of the people, a mission to which knowledge and conscience are to be dedicated. It would seem that these two objectives might form the basis of an ethical dilemma but I do not believe that to be the case, nor do I believe should it ever be the case in respect to clinical investigation.

George James (5) stated that "Much of this research and education must be aimed at finding the keys to prevention of disease, since history has taught us that this is almost always essential before a disease can be effectively controlled." Perhaps this is too narrow a view since many of the diseases which plague humanity may not as yet be preventable but may respond to appropriate treatment. 'Appropriate' surely is a contentious word. How can we move forward in those areas in which our medical knowledge and ability are insufficient. I think it generally can be agreed that every illness is an experiment of nature. If this be the case then the physician-patient interactions in those situations involving routine medical practice for diagnosis and treatment might well be influenced by the very same ethical considerations which we have come to expect when research is involved. Indeed, Shaw and Chalmers (6) espouse the view, which I share, that a well-designed clinical trial is more ethical than the common practice of reliance on clinical impression and past experience which often may be anecdotal. Moreover, in situations in which the effectiveness of the usual medical practice has either not been established, or it appears that a new methodology is promising, it would seem essential to initiate a properly designed and controlled prospective study. The ingredients of such a study are not a subject of this discussion but I think special emphasis must be given to early randomization of patients, the avoidance of an extensive pilot trial the results of which may often be misleading, and the employment of statistical expertise.

Some have raised the ethical issue of "What must a physician do when it is recognized that the available therapy for his/her patients will not suffice." The biblical injunction which establishes the primacy of life clearly is not at odds with the view which holds for death with dignity. The conflict, as so often is the case, is not with the principles but with implementation. Consider the magnitude of the harm if suffering is prolonged or intensified as a result of the research, nor can the pursuit of poor science be justified because death is imminent or otherwise likely.

The foremost initial responsibility of the principal investigators and collaborators is to assure that the research protocol is scientifically sound. The Department Chairman and/or a group of peers must concur in this assessment before any protocol is sent to a review board or study section. Of special importance to all of the reviewers is the evaluation of the risks inherent in the study. The 1975 World Medical Association document, the Declaration of Tokyo, states that doctors should abstain from clinical studies unless they are satisfied that the hazards involved are believed to be predictable, and that they do not outweigh the potential benefits. Research, of necessity, involves the unknown, and thus it is essential that the design of the protocol include analysis of cumulative data by an independent review group to assure that adverse reactions or ultimate consequences do not place subjects at increased risk.

An interesting development in the Declaration of Tokyo has been the recognition of the wisdom to broaden the local institutional review boards to include nonscientists. This has made it necessary for the scientist members of the committee to make clear and simple, if the written protocol does not, the essence of the scientific question proposed for study. I have found such "lay" participation at Mount Sinai exceedingly stimulating, challenging and always helpful. If this experience is generally the case at other institutions, I am confident that liaison with the public will be facilitated, and the credibility of the scientific and medical community will be enhanced. I suggest that we scientists explore the feasibility of exploiting ways by which this growing group can better serve as an effective bridge to and from the community.

The increasing popular emphasis on the importance of individual freedom has led to growing significance of the doctrine of informed consent. The difficulty is the interpretation of the phrase "informed consent." The World Medical Association states that the human subject must be adequately informed of the aims, methods, anticipated benefits, potential hazards and discomforts. The doctor must also inform the subject that he/she is at liberty to withdraw consent at any time without prejudice, and in the federal guidelines, exculpatory language is prohibited. It is stressed that when a subject is in a dependent relationship, or is under duress, the doctor should be extremely cautious when obtaining consent. Leake (7) has pointed out that patients have a right to be informed and to decide themselves regarding their participation. Patients thus incur some degree of moral obligation in respect to the consequences and this position has influenced the concept of compensating injuries sustained by research subjects. But Leake goes on to emphasize that investigators would be unwise to count on such a presumed moral obligation on the part of the subject, "even if every care is taken to avoid harm. Yet trust breeds itself, and while a trustful patient deserves a compassionate physician, a trusting physician *must* assure himself at least of an understanding patient."

In practice, I believe that the degree to which a patient is informed must be tailored to the individual patient. Such factors as the physical and mental status of the patient and the patient's ability to understand sophisticated details are important considerations in the process of obtaining "informed consent." In specific circumstances, discussions with nearest relatives may be essential. In any case, the review committee must be aware of the elements of any informed consent discussion. Interestingly enough, our experience has been that the "lay" members of the committee are extremely sensitive to this part of the written protocol and often suggest ways and words by which to improve the explanation such to reduce anxiety in the proposed subject. It is not unusual to have the investigator's proposed original explanation criticized as being too graphic.

An interesting recent addition to the World Medical Association's recommendations is the recognition that it may be essential to the conduct of some research not to obtain informed consent. In such cases, the specific reasons for this must be stated in the experimental protocol. The review board is specifically charged to review these circumstances extremely carefully.

What are the characteristics of the information to be given to the patient or subject to qualify it as "informed." Firstly, the patient or subject must be legally capable of giving consent. I do not think I need dwell on this point nor do I need emphasize that the patient must be mentally capable of giving consent. Without being overly descriptive, about all I can say, which I think is enough, is that the extent of disclosure needs to be reasonable so that the patient/subject can exercise self-determination. To be sure, reasonableness will be interpreted differently by physicians, investigators, judge, and jury. There is little doubt that in the consent process heavy reliance is often placed on forms which utilize technical language to identify the procedure(s), but it is clear that it is intended that the patient/subject understand the procedure(s) to be employed including those aspects about which uncertainty exists. The process of consent must identify the responsible investigators and coinvestigators. A troublesome detail, but an essential one, is the necessity to provide sufficient disclosure of the risks/hazards, and discomforts, and if possible an estimate of probabilities of such occurrences, especially of the *material* risks such as death, and/or serious complications. I agree with those who advise against total disclosure of every conceivable risk knowing full well that hindsight in a court room setting provides certain legal advantages to the plaintiff. I am not certain that investigators could or can ever safeguard themselves against such a legal assault. To do so could create unnecessary harmful stress and untold anxieties and could as James states "condemn future generations to present levels of inadequate care. The right to informed consent must therefore increasingly be accompanied by the development of strong public opinion for the responsibilities of the present citizen toward his colleagues of tomorrow" (5). I think it appropriate that patient/subject must be assured of the resources available to avoid and/or minimize, and reverse adverse happenstances. In addition, patients/subjects must know that they may withdraw from the protocol at any time without prejudice to their continued treatment as may be routinely available. In special instances, they must know the risks of such withdrawal as well.

One aspect of the consent process has not been given too much attention in routine medical practice but certainly is more regularly done in clinical investigation. This relates to the disclosure of feasible and significant alternatives to the proposed course being recommended. I admit that this is not an easy task but surely the patient or subject needs to have this information if he/she is to make a responsible decision to join with the investigator.

I strongly recommend that the practice adopted by investigators in general that they, as well as an auditor, act as witnesses to the patient's signature on the consent form. To assure the physician that the patient does understand what is being recommended, the patient/subject should be encouraged to ask questions which must be answered frankly. The auditor witness may be very helpful in this respect. This is especially true in the face of recent studies which demonstrate clearly that most patients may not recall the elements of a concerted attempt to provide them with the necessary data and information in preparation for their "informed" consent. In one carefully controlled study, 16 of 20 patients positively denied that certain major items had been discussed when they were reinterviewed four to six months later (8).

I think it appropriate to interject at this point a brief reference to the need to maintain confidentiality of all data as it relates to specific patients/subjects. In my judgment this should be a general procedure, the importance of which becomes obvious in studies involving the use of drugs, genetic relationships, population, and occupational factors. The information being collected in a research protocol may be much more extensive than that ordinarily required and therefore the protocol must contain appropriate safeguards to protect against disclosures not specifically authorized by the patient/subject. This aspect of medical practice and clinical investigation is subject to abuse and careful attention to various details relating to such data is important to both the investigator and patient.

I have attempted with this very quick, and certainly not complete or encyclopedic run-through to stress the view that "informed" consent is in reality an "educated" consent. Ingelfinger (9) has emphasized this view and pleads the cause of a better basis of public understanding of medical research and its requirements. Deception surely is not to be tolerated nor is the process to be equated with that of an elaborate ritual. He states, and I agree, that the subject's only real protection depends on the conscience and compassion of the investigator and his/her peers.

I have not yet focused on the involvement of normal adult subjects, children, infants and/or fetuses in nontherapeutic biomedical research. Data from such subjects are, of course, essential if physicians are to have a better understanding of the nature of disease and the effectiveness of proposed therapy. Suffice it to say that attention to risks and possible hazards is heightened in such protocols and evaluation and review by the institutional and/or independent review board must be intensive and continuous throughout the study.

This surveillance is intended to assure the well-being of those involved. The moral dilemmas in these circumstances are perceived to be acute and more provocative. Each of us participating in the activities of a research review committee cannot escape the feeling of awesome personal responsibility involved in a decision to approve or reject a meaningful project. Truth is not necessarily so evident or so popular as to be the handmaiden of the majority. This is why we must strive to seek truth with a good heart knowing full well that to err is to be human. Society must be prepared to accept this responsibility of unforeseen and unanticipated consequences of the best of science just as surely as it insists on enjoying its benefits.

In summary, I would conclude by saying that sound, meaningful clinical investigation draws on fundamental ethics, moral obligations, values, and judgments. The process which leads to the acquisition of knowledge certain to lead to superior treatment, or the avoidance of inferior medical practices is universally accepted as "good." Society must carefully weigh the cost to humanity when it sanctions possible harm to one person to benefit another. Nor can humanity be enhanced by being callous to the welfare of animals or to the environment. The public's perception and insecurity regarding the possibility of abuse can best be addressed, and confidence instilled, by insistence on better science which must incorporate a sensitive awareness of moral obligations, values, and judgments, and by greater efforts to communicate reliable information in a manner and style easily comprehended by the public. We have witnessed great advances in the past three decades and I remain optimistic that our quest for truth with a good heart will foster dignity and respect and dispel apathy and ignorance.

References

1. Robinson, J.: Christian Morals Today. Philadelphia, Westminster Press, 1967.
2. Leake, C. D.: Moral Muddles in Medicine, Reform Judaism, Vol. 3, No. 2, October 1974, p.1.
3. Stent, G. S.: The Poverty of Scientism and the Promise of Structuralist Ethics, Hastings Center Report 6:32-40, 1976.
4. Konold, D. E.: History of the Codes of Medical Ethics. In *Encyclopedia of Bioethics*. Free Press, Georgetown University, 1977.
5. James, G.: Clinical Research in Achieving the Right to Health, Ann NY Acad Sci 169:301-307, 1970.
6. Shaw, L. W. and Chalmers, T.C.: Ethics in Cooperative Clinical Trials, Ann NY Acad Sci 169:487-495, 1970.

7. Leake, C. D.: Ethical Theories and Human Experimentation, Ann NY Acad Sci 169:487-497, 1970.
8. Robinson, G. and Merav, A.: Informed Consent: Recall by Patients Tested Postoperatively. Personal Communication.
9. Ingelfinger, F. J: Informed (But Uneducated) Consent, Editorial, N Engl Med 287, 465, 1972.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 5, September-October, 1977
Printed in U.S.A.

Health Care Delivery: Harsh Realities and Uncertain Ends

MICHAEL G. MACDONALD, I.D.

> The mystery of change and motion still vexes the minds of men as it baffled the Eleatics of old in the beginnings of recorded thought. I make no pretense of having given you the key that will solve the riddle, the larger and deeper principle that will harmonize two precepts which on their face may seem to conflict, and thus to result in an antimony. I can only warn you that those who heed the one without honoring the other will be worshipping false gods and leading their followers astray. The victory is not for the partisans of an inflexible logic nor yet for the levelers of all rule and all precedent, but the victory is for those who shall know how to fuse these two tendencies together in adaptation to an end as yet imperfectly discerned. *Justice Benjamin N. Cardozo.*

The problem of rising health care costs has become a source of great public concern. Costs continue to increase at a rate faster than the consumer price index and constitute a larger and larger share of the gross national product. Public programs, faced with local fiscal problems, are under great strain to keep pace. And, we are told, General Motors must spend nearly as much for health insurance for its employees as it does for steel. It is now indisputable that, like other segments of our economy suffering shortages of raw materials, the financial resources that are available to pay for health care are finite.

Most Americans are not accustomed to living in a world where resources are limited. Ever since we learned to read the upward slopes of those brightly colored graphs in grammer school, we have been taught that our strength as a nation and our progress as a people are measured by how much more we produce and how much more we consume. Our expectations have been fueled by prospects of a boundless economy and seldom have we questioned whether there would be sufficient resources for tomorrow's needs. It is difficult for us to imagine a limit to our standard of living. In the delivery of health care, in particular, if a new hospital or new piece of equipment was necessary, we would have it and it would usually be the best and most modern money could buy. But the limitations on growth in the health care field, as elsewhere, are very real. For the first time, we must come face to face with questions which for Americans are very difficult: how do we allocate limited resources within the health care delivery system, how much care is appropriate, who shall have access to it, what is the appropriate size of the system and what shall its components be?

From the Legal Department, The Mount Sinai Medical Center, New York, N.Y. 10029

Request for reprints should be sent to: Michael G. MacDonald, Legal Department, The Mount Sinai Hospital, Fifth Avenue and 100 Street, New York, N.Y. 10029.

Perhaps not surprisingly, efforts to deal with the underlying social policy questions largely have been exercises in avoidance. All too often the focus of government has been on the containment of costs as if it were a simple mathematical problem without any social policy implications. Allegations of inefficiency, waste and abuse crowd the headlines and have left the impression that if we could develop an effective cure for these maladies, it would be business as usual with no need to make hard choices regarding quality or program content. For its part, the health care industry has steadfastly resisted with "inflexible logic" the imposition of any limitations as a threat to those standards of excellence and medical progress which Americans have always demanded.

The chaos which has ensued has not been pleasant. Nowhere is this more evident than in New York, where a virtual state of war exists between the providers of health care and the State government. Faced with unilateral limitations on reimbursement, imposed in many cases retroactively at the end of the budgetary year, health care providers have resorted increasingly to litigation. The result has been an array of lawsuits challenging a variety of government policies which has led to a further hardening of positions (1). The public, upset with high costs and with the increasingly depersonalized care they receive, has found itself in a confused and bilious mood. There is reason to believe that the battle will soon be joined at the federal level (2).

This state of affairs should be cause for great concern. The consensus necessary to meet the complex, difficult challenges posed by an expanding medical technology and an increasing demand for health care in the face of limited financial resources has broken down. The government seems to have adopted the blindfold as an instrument of policy; and providers, not known for their willingness to compromise, are caught with having to defend a system which even they admit must now be changed. Rather than attempting to reason out solutions based on a hard look at the facts, health care policy is being developed with a total disregard for the underlying causes of the problem of rising costs, the goals of the system and concern for the variety of societal interests which are affected by governmental policies. Perhaps most importantly of all, the integrity of the processes by which health care decisions are made has all but collapsed. Unfortunately, it is in the courtroom arena that much fundamental health care policy is thrashed out.

This is an article of reflections by a lawyer who has spent a considerable amount of time on the battlefields dreaming of more peaceful times. The inability of the government and providers to close forces in attempting to resolve the many fundamental policy issues involved in our changing circumstances, the lack of fairness in the way in which decisions are reached and the refusal to move toward more creative, albeit more politically difficult, solutions are concerns which touch us all and which have ramifications far beyond the health care area. So too does the decline in excellence in our health care system which threatens to become pandemic.

Some Facts about the Present System

It would be nice to have the luxury of being able to discuss the health care system as if we were starting at the planning board from scratch. Unfortunately, we must take the system as we find it, and any discussion of our current dilemma and the underlying policy issues must start with a look at where we are now.

a. Medical Technology

We are all familiar with the litany concerning rising health care costs. Total health care expenditures have nearly quadrupled since 1965, up from $39 billion to nearly $140 billion today. During the 1960s, inpatient hospital expenses doubled within 8 ½ years, which is an annual rate of growth of over 10%. In the 1970s, these expenses have already doubled and the percentage increase of 1976 expenses over those incurred in 1975 was over 15% with a similar increase forecast for 1977. Government insurance has assumed an increasing share of this burden. Between fiscal years 1967 and 1975, the cost of providing Medicare services increased $10.4 billion from $4 billion to $14.4 billion. The costs of Medicaid expenditures, which are borne in part by the states, increased $9.8 billion between fiscal years 1967 and 1975 from $2.3 to $12.1 billion. Although there is no doubt that much of this increase has been caused by inflation in the economy generally, these increases are substantially greater than the general rate of inflation and represent a steadily increasing share of the Gross National Product (3).

Health care costs are frequently measured in terms of average expenses per day and increases in costs are measured by comparing per diem expenses from year to year. It is natural for the public to assume, therefore, that a 10% rise in per diem expenses means that an appendectomy which cost $100 last year now costs $110. Yet this is clearly not so. Comparisons of *average* costs of today's health care to the costs of yesterday's health care fail to reveal what is perhaps the most significant cause (other than inflation) of the rise in health care costs: the truly revolutionary change in the nature of the health care product.

Not too long ago many illnesses, notably heart disease and cancer, were invariably hopeless. A heart attack patient, for example, would survive or die largely on his own; there was very little medicine could do. Open heart surgery, cardiovascular surgery, implantation of pacemakers, and cardiac intensive care units were unknown. Today these are taken for granted. In fact, modern medicine has evolved so rapidly in the last several years that there are now very few diseases which physicians are willing to call "incurable" (4). Thus, in the treatment of cancers, although no one, wished-for panacea has been found, combinations of new diagnostic techniques, surgical procedures, and chemotherapy have dramatically improved remission rates of many cancers, including childhood leukemia, which a decade ago were certain to kill.

The list of these major technologic developments is quite long indeed. Other developments include organ transplantation, renal dialysis, nuclear medicine, and microneurosurgery, to name a few. There are also many innovations and improvements of a less dramatic nature. Diagnostic techniques, in particular, have vastly improved, from new radiologic procedures, such as angiography, to the spectacular developments of nuclear medicine, including nuclear cardiac catheterization. Even the analysis of bloods and urines continues to yield more and more clues to disease through the development of more sensitive and sophisticated equipment. In short, medicine is in a constant state of growth and improvement and there are very few areas which technology has left unchanged.

This "intensification" of services has taken place not only in the sophisticated urban medical centers but in the nation's thousands of community hospitals as well. There are now many more specialized units and laboratories in community hospitals than in the recent past, and this trend is continuing. Similarly, the scope of programs in community hospitals has continued to expand to permit providers to render the best, most modern care possible (5).

Not only have the physical plants of hospitals necessarily become more complex, but hospitals have eliminated many of the discomforts and infectious disease hazards that characterized hospitals not long ago. Open ward areas have given way to private and semiprivate rooms with superior sanitary and other facilities which are now mandated by most state hospital codes (6). Obviously, this "upgrading" represents a substantial investment of capital which is reflected in annual operating expenses.

Thus, in sum, a primary cause of rising hospital costs is attributable to changes in health care product. Moreover, and of paramount importance from the point of view of future policy, there is no doubt that technology and health care intensification will continue to grow indefinitely unless limited in some fashion. One need only contemplate the development of the artificial heart, the developments evolving out of the "new" science of nuclear medicine and the phenomenal possibilities of DNA research to see that the technology revolution will continue and probably quicken.

b. The Medical "Market"

There are significant features of the medical economy which have permitted health care technology to improve so rapidly. In a conventional market, the consumer of a product makes a free choice as to how to spend his dollars in terms of his own assessment (perhaps with the "invisible hand" of Madison Avenue) of his needs. In doing so, he presumably is able to assess both the quality and price of the product against the quality and price of competing products. Knowing this, a producer competes for those consumer dollars by attempting to produce superior products at the lowest prices.

Not so in the health care field. First, health care is "marketed" through the health care provider (usually the private physician but increasingly by the institutional provider). Once the patient/consumer contacts the physicians, the physician becomes a caliph in the decision-making process who determines both the needs of the patient for the health care product as well as how much of that product the patient should consume. This includes such key decisions of whether hospitalization is required, what level of tests and procedures shall be performed, and how long that person should remain in the hospital. The authority of the physican is so pervasive because of the faith and trust which have traditionally been accorded to him (7) as well as the difficulty, indeed, virtual impossibility, of the consumer in making informed judgments about the quantity and quality of services (although most patients want the "best") that are needed.

Second, the consumer/patient's financial incentives to limit his or her "consumption" of health care services have largely been removed by the availability of private insurance schemes, such as Blue Cross/Blue Shield, and government programs, such as Medicare and Medicaid. Health care expenses are not a direct expense of the patient and thus he has a blank check to purchase the best care he can. For the same reasons, there are few economic limitations which would affect the physician's judgments in making his recommendations. He provides, and instructs hospitals to provide, what he deems necessary without regard to price. Because of the physician's dominant influence on hospitals, the physician can demand the best facilities and the most modern equipment and technology, again, largely without any limitations as to what the costs may be.

When the foregoing "market" characteristics are combined with hospital reimbursement schemes which are essentially cost based, it should be easy to see why technology has advanced so rapidly: there simply have been no financial restraints on the *physician* to supply whatever level of demand the *physician* has thought necessary.

We might pause here briefly to ponder this very unconventional economic fact, namely, that the physician is the judge of both ends of the law of supply and demand. Not unexpectedly, this state of affairs, coupled with the rising expenditures it has produced, has inspired some critics to accuse health care providers of waste and abuse and to suggest motivations of the lowest magnitude. Often medical advances are described as "expensive," as if to suggest that these new therapies are unnecessary and bad, and the expansion of medical complexes is seen as an extension of the egos of hospital trustees (8).

No doubt there are abuses, especially in the Medicaid program (which, one is constrained to point out, is administered with total neglect by state and local governments), no doubt the allocation of resources could have been planned better and with greater coordination among institutions and no doubt providers could achieve greater efficiency in their operations (as some hospitals in New York are demonstrating, where the fiscal crisis is more acute). We must also recognize that there are probably inherent conflicts of interest in many of the choices which physicians, principally surgeons, make (9).

But surely the technologic advances of recent years are overwhelmingly the result of well-intentioned physicians trying to find cures to the difficult problems of disease and to do their best by their patients. It is easy to argue in the abstract that we have too much expensive equipment, too many scanners, too many new x-ray machines, too many intensive care beds. Yet when you look at the miracles this technology accomplishes on a case by case basis, it is hard to argue—especially if one of those cases is a relative or friend—that they are unnecessary. Indeed, most people, when seriously ill, want and demand the best and physicians and institutions have responded. It is also important to recognize that much of this technologic revolution is taking place in the large urban medical centers, which are able to gather the best intellects and most highly motivated physicians. Often these physicians are paid salaries which are substantially less than what they could earn in "private" practice.

I suspect that much of the criticism of physicians and hospitals stems from an increasing frustration with the depersonalized brand of medicine which specialization and technology have in part been responsible for bringing about. Perhaps, too, the view which saw physicians as pillars of trust and respect is also beginning to crumble in the face of a more consumer-oriented public. This is compounded by the arrogance of many physicians who cling to older attitudes of physician omniscience (10). In any case, although it is certainly easy to identify with an increasingly frustrated public, the endless flow of invectives and broad sweeping criticisms of hospitals and physicians tends to obscure the irreducible fact that *the practical application in medicine of burgeoning knowledge and technology is virtually unlimited and that, for better or for worse, the health care system could absorb an unlimited quantum of resources to fuel these advances* (11). The question of how to plan these "unlimited" advances in the face of "limited" financial resources in a fashion that is consistent with the public interest is a major question which in today's realities cannot be ignored.

c. *Egalitarianism*

The impulse toward egalitarianism in health has been steady. Unlike many facets of our society, health is increasingly seen as a fundamental right of all citizens. Although there is much to criticize in the response to satisfy this demand, the health care delivery system reaches more people today than ever before. Over 23 million people were afforded coverage under the Medicare and Medicaid programs initiated in 1967 and the number of those eligible for these programs continues to increase. In the case of Medicaid, for example, there has been over a fourfold increase in recipients and the number of states and territories with Medicaid programs has increased from 7 to 53. In the case of Medicare, an additional 4.7 million persons are eligible in 1975 compared with 1967 (12).

The scope of benefits has also significantly increased. The Social Security Amendments of 1972 added provisions to the Social Security Act which expanded coverage under Medicare of individuals under age 65 who had been entitled to social security or railroad retirement disability benefits for 24 months or more as well as established an extended renal dialysis benefit to individuals suffering from chronic kidney disease. The primary effect of these legislative changes was to increase the number of people eligible for Medicare at an additional cost of approximately $1.1 billion in fiscal year 1974 and about $1.6 billion in fiscal year 1975 (13).

As the egalitarian impulse continues to grow, obviously the system will be increasingly utilized. Moreover, we also know that large segments of the population already eligible for coverage do not use or underutilize the system. As "preventive" and other public health efforts succeed in reaching those not currently availing themselves of the health care system, we can expect a further increase in demand. Finally, since our population is becoming steadily older, we can expect usage of the most sophisticated therapies and facilities to increase.

The point here is twofold: First, part of the historical rise in aggregate health care costs can be attributed to an increase in the numbers served by the system. Second, for purposes of determining the configurations of future policy, we must understand that more egalitarianism—a highly desirable goal (14)—coupled with successful efforts to bring those already covered into the system and the fact that our population is becoming older will result in even higher demand and utilization. This naturally will create substantial upward pressure on costs even assuming that the quality of the product delivered remains constant. This demand, coupled with the surging pressure of increased technology, obviously forces very difficult problems of allocation upon us.

d. Lack of Planning

The health care delivery system developed at a time of little regulation and planning. Since the health care bill was, in general easily manageable by those who used the system, there were few financial constraints or other limitations on the development of new technology, the construction and location of facilities and the training and location of physicians. As a result, it is estimated (judged by today's harsh realities) that there are nearly 5,000 excess beds in New York City and nearly 100,000 nationally. Many of these beds are in small inefficient hospitals which the system has simply outgrown. We also know that there are large concentrations of doctors in urban areas, dislocations of physicians within some urban areas and an inadequate distribution of physicians in rural areas. In the past, regionalized planning of health care was not seen as a goal, perhaps, in part, because care was not yet so highly specialized that regionalization was really necessary. Today, of course, it is indisputable that not every institution can become a tertiary care center and that resources must be managed on a regional basis.

In addressing ourselves to the question of how to meet future needs, it is obvious that we must also address ourselves to the discontinuities in the present system. We shall see that efforts to do this have not been successful and as a consequence all hospitals, both efficient and inefficient, both needed and unneeded, exist side by side in an uneasy disharmony.

e. Other Reasons Why Costs Have Increased

Another significant feature of the health care system, which is related to the intensification of the health care product, lies in the fact that the provision of health care is labor intensive. New technology in health seldom replaces people; rather, the introduction of new techniques, such as those recently introduced in the fields of radiology and nuclear medicine, usually requires the addition of people with a much higher degree of skill and sophistication. This is a major reason why, in the last decade, the number of persons employed in the health care system has increased by 43.5 percent and the number of employees per patient day have increased from 1.5 to 2.7 (an 80 percent increase) (15).

No doubt some of the increase in the total costs of labor can be attributed to the relatively high wage increases won by employees. These increases often appear to be dramatic, but it must be borne in mind that for decades the hospital employee was underpaid relative to industry norms. In urban centers, these increases have now put labor on a par (or better) with similarly situated employees in almost any other sector of our economy. With the extension of the National Labor Relations Act to the health care industry in 1974, we can expect substantial union activity to take place and for the rest of the hospital industry to catch up to the urban centers. This will obviously contribute to further rises in health care expenditures.

It is also important to recognize that although in many respects the health care market is "unconventional," hospitals, like any industry, must purchase the materials they use from third parties. A large part of hospital costs are not immune from the inflationary trends which have afflicted the economy generally. The dramatic increases in the costs of such items as food, fuel and electricity—of which hospitals are large consumers—have had a devastating impact on hospital costs. Although it can be argued that manufacturers have exploited the health care market very successfully and although it is perhaps true that health care providers have been remiss in aggressively pursuing the most competitive prices, to a very high degree, providers have little or no control over the prices they pay for the goods and services they must buy.

Although health care providers are often the object of attack, medical equipment manufacturers and drug companies are seldom mentioned. One of the obvious questions which we must grapple with is whether we can realistically impose controls on the revenues of providers without also imposing controls on the prices providers must pay to their suppliers.

f. The Government Framework

It is somewhat encouraging to note that in a broad structural sense the government has begun to put in place the various pieces of the puzzle needed to deal with these problems. The National Health Planning and Resource Development Act of 1974 provides a structure for the overall national planning of health care delivery. Regional planning agencies have finally been established under the provisions of this Act. The Professional Standards and Review Organizations and utilization review committees of hospitals required by the 1972 amendments to the Social Security Act are beginning to develop utilization and other professional performance standards. The Health Professions Educational Assistance Act of 1976 will attempt to address the questions of what types of physicians should be trained and where they should practice. The Hill-Burton Program remains in the statutes to provide assistance for facility construction. And, of course, the mechanisms for the financing and control of research through the National Institutes of Health have long been in place as has the mechanism (the Food and Drug Administration) for control of the testing and manufacture of drugs and equipment.

There are two very major reasons why the government's response has been disappointing. First, this structure has not produced an integrated national policy toward health care planning and the delivery of services. The states, certainly in New York, at least, have dominated the structure. Important policy questions have been largely avoided in favor of the machinations of agencies of state and local government. Indeed, faith in this federal superstructure as well as in local mechanisms to deal with these questions has sharply diminished. Second, the cornerstone of any national health policy is missing: a consistent approach to the financing of health care provider costs which is integrated with other health care policies. In the absence of such a policy, chaos has ruled. It is worth looking at this latter point a bit more closely.

Hospitals are faced with a maze of confusing and often conflicting reimbursement regulations and related controls (16). Medicare pays health care providers based on their reasonable costs, Medicaid reimburses pursuant to a variety of state formulations which frequently include the establishment of "prospective" rates, and Blue Cross and other insurance schemes pay for costs through yet another series of reimbursement principles. These multiple, conflicting arrangements fail to take into account the true nature of a provider's costs and are seldom adequate to meet the institution's financial requirements. As a result, institutions are forced to make up the income short-falls by engaging in price discrimination against self-pay patients and other third-party payers. Moreover, there is no coordination of reimbursement with the planning of health care programs and no integration of reimbursement for ambulatory care with inpatient reimbursement which has thereby encouraged the use of more expensive inpatient care.

The response in New York has been especially disappointing. New York is one of the first states to come face to face with severe limitations on resources in the midst of a fiscal crisis. Thus, the normal political restraints which often impede effective planning were greatly negated by the necessity to take immediate action. Yet despite this "opportunity" to restructure and better plan the system, the State's policy has focused exclusively on the containment of costs without any apparent concern for the impact those policies might have on the provision and quality of services. This failure to integrate planning with reimbursement is clearly illustrated by the fact that the State has neither attempted to close unneeded beds, which it estimates at 5,000 in New York City alone, nor addressed the enormously inefficient New York City municipal hospital system—whose costs as to which no independent auditor will certify.

Where Do We Go from Here?

It is clear that the problems of rising health care costs are enormously complex. There have been few limits on the intensification and improvement of the health care product, through technology or otherwise, and the health care system could absorb a virtually unlimited amount of resources. It is likely that, given the financial resources to do so, providers will continue to improve and intensify the health care product. By a parity of reasoning, although there is much room for improved efficiency in the health care sector, limitations on increases in funding will have, intentionally or not, a significant impact on the type of services offered.

In the days of unlimited cost reimbursement, decisions as to how to allocate health care resources, what levels of care and utilization were appropriate and how to plan the development of new technology were left largely for physicians and hospitals. Society *implicitly* concurred in these and many other fundamental policy choices by its acceptance of the way in which the medical "market place" functioned. But the pressures of an expanding technology coupled with demand for increased utilization have now collided with the realization—as difficult as it may be for Americans to accept—that our resources are finite and that we cannot have everything that we want in the way of health care. Thus, decisions which were implicitly made in the past are today thrust onto a more conscious, *explicit* level. The decisionmaking process has shifted away from the physician, and it is still not clear what the final shape of this process will be.

As we face the reality of finite resources, many very fundamental questions are raised: How and to what extent do we limit technology? How do we protect and expand the egalitarian principle of adequate medical care for all who need it? What are appropriate levels of utilization? How do we assure that there will be adequate health care facilities available and an adequate supply of physicians to underserviced areas? How do we continue to train physicians and in what specialties? Is the fee for service still realistic?

Some have raised even more basic concerns: Does the health care system have any real impact on health (17)? Should we direct the tens of billions of dollars we spend on treating disease to basic scientific research and to the finding of new cures and new immunizations (18)? Should we divert more of these resources into preventive efforts, such as cleaning up the environment of the contaminates which cause much of our modern society's serious disease? Should medical schools shift their orientation from learning about disease to learning more about health and nutrition? Should we impose limits on the vast amount of health care resources which are now used to postpone for relatively short periods the inevitable deaths of terminally ill patients? Is there a time to die beyond which the intervention of health care is not appropriate?

And lastly, how are all of these questions to be resolved?

Although the present health care delivery system can give us our present location and possibly set our initial bearings, the ends are "as yet imperfectly discerned." Anyone who thinks he knows the direction is likely to carry us to the worship of intolerable rigidity at a time when flexibility and adaptability to changing circumstances is necessary. We must constantly seek to learn more about health and the health care system and be prepared to adapt and make adjustments as the data shed light on new directions. Of fundamental importance is the need to develop a process for decisionmaking whereby the issues can be debated and the broad spectrum of societal interests affected taken into account. Without faith in this process, the consensus necessary to arrive at the ends will never coalesce.

In sum, as we begin to struggle with the problems of finite resources, it is important that we proceed with caution and that we resist the temptation for quick solutions that are politically expedient. There are no simple answers to any of these problems and we must afford great leeway for experimentation, reevaluation and further experimentation as the system evolves through the vast sea of changes that lie ahead.

Nevertheless, there is a great deal that can be done as a short-range strategy. Several immediate steps can be taken to alleviate some of the building pressures on the system and provide a framework within which the larger policy issues can be debated. These include, briefly:

1. Shut Down Unnecessary Beds and Programs. The system must be reduced to eliminate excess capacity. The estimated 5,000 unneeded beds in New York City and 100,000 in the nation should be closed immediately. The burden of these beds on the rest of the system and on society is unconscionable in the face of pressing needs. Similarly, underutilized programs should be closed or severely penalized for inefficient operation. These tough political decisions must be made lest the system slip hopelessly toward mediocrity.

2. Planning Mechanism Strengthened. The planning function of government should be strengthened to assure that future programs are needed consistent with the public interest. Furthermore, existing programs must be measured pursuant to objective criteria, which hopefully will emerge as data with respect to the delivery system are developed, to make certain they continue to satisfy community needs. The broad structure set forth in the National Health Planning and Resource Development Act must be given teeth. Obviously, in major metropolitan areas we must begin to move toward greater regionalization of resources. Since we cannot afford to have a major tertiary center in every community, efforts should be increased, perhaps through incentives or government grants, to make the expertise of large urban medical centers more cost-efficient by making it available to outlying and rural areas through the increased use of computers and audiovisual techniques. These centers must become the central hub for the coordination of health planning.

In advancing the foregoing suggestion, we must recognize that by having a highly planned and regulated health care system, we run the risk that it could become in time a government system. No doubt this would stifle creativity, drive competent staff from the industry and destroy the multiplicity which, as in other areas, has made the health care system viable. Moreover, one has to be very concerned with the quality of the regulators and their ability to be the principal arbiters of the many fundamental choices affecting broad societal interests which must be made. However, we must take the system as it is and it is not realistic to expect that in the short range the job can be done without government regulation. Perhaps in time coalitions can be forged which better serve the public interest.

I am also mindful that some have argued for more competition in the health care industry (19). Implicit in these arguments is not only the distrust of the wisdom of government regulators but also the assumption that the market place is the appropriate vehicle to determine the scope and quality of services to be offered. The HMO experiment is seen as the model which should be expanded and built upon. There are also proposals to permit third-party payers to act as surrogate "consumers" by choosing from among competing providers which shall render care to their subscribers.

One of the difficulties with these approaches is that hospitals are not easily able to open and close their facilities and fire and rehire qualified staff depending on yearly competitions for the "business" of a third-party payor. If a hospital were to lose a significant part of its patient load one year, it would not be a viable competitor the next. In short, this type of competition could easily tend toward the same type of monopoly it is designed to challenge and in the process destroy needed facilities. One must therefore proceed very cautiously lest this type of competition generate tremendous dislocations in the system and lead to chaotic resource planning. Also, "competition" often tends to focus on price, particularly when other characteristics of the product are difficult to measure. This is especially so in the area of health care and we can be legitimately concerned that increased competition may adversely affect quality by permitting price to dominate the process of product selection. This is not to say that some competition should not be attempted. However, for the time being at least, these efforts should be attempted primarily in the area of ambulatory care.

3. *Reimbursement*. There are several fundamental changes in the reimbursement system which must be made:

(a) The planning process must be integrated into the reimbursement process. A cardinal principle of any reimbursement system must be that programs and services approved as necessary by the planning agency must be adequately reimbursed. A health care system which has reasonably "healthy" components is much better than a larger system, the constituent parts of which are inadequately financed. A provider should not be forced to increase its charges to other categories of users to make up the short-fall of inadequate reimbursement received from other third-party payers or to eliminate services which might well be needed by the community. In this respect, an institution's costs should be monitored to ensure that pursuant to objective criteria they are efficiently incurred. Management engineering techniques should be applied for this purpose as well as criteria developed from the PSRO and utilization review programs. If it develops that a program has ceased to be efficient or is no longer needed it should be closed with an opportunity for the provider and the community to present its views.

(b) We must begin to move away from per diem formulations and generalized approaches to reimbursement which treat providers alike (20). Providers are different, have different patient mixes and offer different services. One approach would be to establish a rate-setting commission whereby a hospital would submit its proposed rates in advance to a separate agency established for that purpose. The hospital would be required to develop these rates and to state its program and budgetary assumptions. This rate would be "tested" by the state by several measurements, including the costs of doing business, efficiency of operation, occupancy levels, type and quality of care offered and capital requirements (21). A hospital would also be required to justify any increases beyond increases in the inflation of the economy generally. This would enable both the agency and the hospital to take into account the intensification of services which its particular programs require. These determinations would all be made in advance of the coming year so that a hospital would have a clear idea of the resources with which it has to work. There should be a single set of reimbursement requirements to ensure the integrity of the budget revenue forecasts and to permit more accurate planning. Since patient mixes, utilization and other key factors affecting hospital costs change from year to year, this more precise individual approach would permit more accurate planning and avoid the inequities which result when hospitals are lumped together for reimbursement purposes.

(c) Incentives toward efficiency should be developed and established. Although there is a limit to how much in savings can be achieved by measures designed to improve efficiency, clearly, increased productivity should be encouraged and where achieved rewarded. Incentives should be developed for experiments with shared services, group purchasing and other interinstitutional arrangements. One possible approach would be to permit an institution to share directly with the government in the cost savings it is able to generate. In developing such incentive programs, one must, of course, be careful that quality is not sacrificed. In short, care must be taken lest the incentives be too effective.

4. *Reimbursement for Ambulatory Care.* There must be adequate reimbursement for ambulatory care. Ambulatory care is of increasing importance in any integrated approach to the provision of health care and providers should be free to offer the type of care that is appropriate to the needs of patients. Often these choices are circumscribed by inadequate reimbursement for ambulatory services and by the conflicting methodologies that currently prevail. This discourages efficient inpatient utilization and imposes inappropriate restraints on the planning process. If only the most serious cases are hospitalized—a clear goal of any rational system—then inpatient costs on a per diem basis will increase, as will length of stay, even though society as a whole will be paying less for hospitalization. A hospital will be harmed if reimbursement methodologies do not take this into account. As indicated, greater experimentation with HMO-type arrangements and perhaps limited competition among providers should be attempted and carefully monitored. If successful, these efforts should be expanded.

5. *Use of Paraprofessionals.* Paraprofessionals and so-called physician extenders can and must play an increasing role in the delivery of health care. This is especially true in the provision of ambulatory care, whether it be in the hospital clinic or the physician's office. There is no reason why many of the relatively routine tasks and even some direct primary care now performed

by highly paid physicians cannot be performed by trained paraprofessionals. Even in the provision of inpatient hospital care, paraprofessionals can assume many of the simple tasks which command so much of the physician's time and which prevent him from maximizing the extent to which his more sophisticated expertise is made available to patients who need it. Government should provide incentives for the training and use of these important members of the health care team.

6. *Continue Efforts to Develop Meaningful Data with Respect to Utilization and Quality of Care.* It is shocking that we still have no way of measuring health care outputs. Not only must more accurate measurements of the health care output be devised to assure the efficient production of hospital services, but we will continue to flounder in attempting to come to grips with basic health policy issues unless we have a way of measuring the impact of medicine on health. Despite the hue and cry that accompanied the introduction of the utilization review and PSRO programs, there are real, tangible signs that these programs work. They should be strengthened and greater efforts should be made to make physicians more aware of the impact their decisions have on the utilization of the limited resources of the health care system. The days of unlimited tests and unlimited services are over and physicians must exercise much greater restraint in their choices. If they do not, these judgments will be imposed upon them by government bureaucrats without their participation.

7. *Assure Due Process.* The system must be a fair system. The number of lawsuits in New York and elsewhere by health care providers against state governments is in part the consequence of state action taken arbitrarily without an opportunity for those most directly affected to be heard. The consensus necessary to make meaningful changes in the system will only develop if all interests are appropriately taken into account.

8. *Eliminate Fraud and Abuse.* Fraud and abuse should not be tolerated. Physicians of good conscience are being tainted by the avarice of a few, many of whom are not even physicians. State and local governments need not wait for federal legislation, but should strengthen their own criminal laws and enforcement units. Just as enforcement of the federal antitrust laws was not taken seriously until the first white-collar offenders were sentenced to prison terms, it will have a salutary impact if judges treat Medicaid fraud and similar types of abuse as serious crimes. Physicians, medical societies and hospital associations must take public positions in urging that these abuses be dealt with harshly.

9. *Public Relations.* Hospitals and physicians must do a much better job of educating the public as to the reasons for rising health care costs and the nature and limitations of modern medicine. Government is now largely able to have its way because of the lack of public support for the positions of hospitals and physicians. As we face the difficult choices ahead, the public must be educated and kept better informed so that they can participate in a more intelligent and meaningful fashion through their elected representa-

tives or otherwise. And, at the risk of being sophomoric, physicians and institutions must mix with the superb technical care they dispense a larger portion of caring and concern for the patient as a human being.

Conclusion

In many respects, what we see happening in the health sector is a reflection of what is happening in other sectors of the economy. We can no longer look forward to unlimited growth and must come to grips with the difficult problems posed by finite resources in the face of expanding technology and increasing needs. In the health sector, these problems are enormously complex and they strike at many fundamental assumptions concerning health and the health care delivery system which in the past were implicitly accepted. We must now make choices as a society which we have never before confronted on a conscious level.

Our system of laws has provided us with a process whereby we have been able to order our priorities and resolve the many problems, some often tumultuous, which have confronted us as a people. The genius of the system is that it has been flexible and capable of vital adaption and readaption on an incremental basis to changes and the emerging needs of society. It has always depended on the consensus, embedded perhaps in the pragmatism of the American people, that as long as the system is fair and administered with a high degree of integrity, the results it produces will be respected. One of the most fundamental currents in our society today, exemplified in the health care sector, is an erosion of our faith in that system. And if the government itself disrespects that system, then there is no system, there is no law.

The challenges that lie ahead will pale in significance if we permit these fundamental processes to deteriorate. The summons to a rededication to the orderly process of principled decisionmaking still presses for a response.

References

1. See, *e.g., The Medical Society of the State of New York v. Toia,* CCH Medicare and Medicaid Guide, ¶28,364 (E.D.N.Y. 1977); *Hospital Association of the State of New York et al. Toia et al.,* CCH Medicare and Medicaid Guide, ¶¶28,026, 28,304 (S.D.N.Y. 1976). New York is not alone. See *Illinois Hospital Association et al. v. Walker,* CCH Medicare and Medicaid Guide, ¶28,371 (N.D. Ill. 1977); *New Jersey Hospital Association v. Klein,* Civil Action No. 76–64 (D.N.J. 1976); *Robinson v. Maher,* CCH Medicare and Medicaid Guide, ¶27,707 (D. Conn. 1976); *Wisconsin Hospital Association v. Schmidt,* CCH Medicare and Medicaid Guide, ¶27,818 (E.D. Wisc. 1976); *California Hospital Association v. Obledo,* CCH Medicare and Medicaid Guide, ¶27,998 (C.D. Calif. 1976); *Benton and Wisebacker v. Rhodes,* CCH Medicare and Medicaid Guide, ¶28,025 (S.D. Ohio 1976); *Massachusetts General Hospital v. Sargent,* 397 E. Supp. 1056 (D. Mass. 1975).
2. At the time this article went to press, President Carter proposed across the board ceilings on health care expenditures and Senator Talmadge introduced reform legislation to limit government expenditures under the Medicare and Medicaid programs. Already the battle lines are forming.
3. "History of the Rising Costs of the Medicare and Medicaid Programs and Attempts to Control These Costs: 1966–1975", Report to the Human Resource Task Force, House Committee on the Budget, by the Comptroller General of the United States (U.S.

Government Printing Office 1976) (hereinafter "Comptroller's Report"). And see generally, Council on Wage and Price Stability, The Problem of Rising Health Care Costs (U.S. Government Printing Office 1976); Chartbook of Federal Health Spending 1969–1974, National Planning Association (Washington, D.C. 1974).

4. The consequence of the technological advances of modern medicine has almost theological implications, and questions of death and dying have become more troublesome then ever before. As technology advances, the capacity to prolong life and to postpone death increases. These cures are often not complete and increasingly our aging population has become dependent on the health care system for "maintenance" and continuing therapy. Not only is this technology enormously expensive, but it also often prolongs the agony associated with protracted terminal illness which places great strain on patients and their families. How do we allocate resources among the critically and terminally ill? Should we keep people functioning in a vegetative state? Is there a point in the process of aging and dying beyond which the intervention of medicine should not be permitted? Who should participate in balancing and resolving these very difficult ethical and practical questions? It should be noted that the courts have begun to agonize over these questions (see *In re Karen Quinlan*, Supreme Court of New Jersey, 1975, which struggles to define human life in terminology like "cognitive sapient state") and that in at least one state the "Living Will" has been enacted into law (California Health and Safety Code, Chapter 3.9). Are we moving too fast? Should the courts and the legislatures stay out of these areas until we know more about them and the public becomes better educated as to the issues involved? See, generally, "Death and Dignity", Report of the Committee on Medicine and Law of the Association of the Bar of The City of New York, Vol. 32, No. 3 (March 1977); Macdonald, Michael G. and Meyer, Kathryn C., "Defining Death", The Mount Sinai Journal of Medicine, Vol. 43, No. 3 (May-June 1976).
5. Cf., Philip, Joseph, "A New Perspective on Cost Inflation", Hospitals, Vol. 47 (October 1, 1973); Berry, Ralph, "Perspective on Rate Regulation", Controls on Health Care, Institute of Medicine, National Academy of Sciences (Washington, D.C. 1975) (hereinafter referred to as "Institute of Medicine"), pp. 109–115.
6. Prior to World War II, 20–30 bed wards were frequently jammed with twice the number of patients they could accommodate, and often patients were placed in corridors. There were never enough doctors, nurses and other staff and the most inhumane conditions prevailed. This was, of course, at a time when there were no effective therapies against many of the most common infectious diseases and when "isolation" was the only restraint against epidemics. See, Thomas, Lewis, "Limited Hospital Success Tied to Incomplete Technology", Hospital Tribune (February 1974).
7. See generally, Reinhardt, Uwe E., "Alternative Methods of Reimbursing Non-Institutional Providers of Health Services", Institute of Medicine, p. 144 et seq.
8. Berry, *op. cit.*, pp. 111–112.
9. Whether this leads to "unnecessary" surgery is still a matter of heated debate. See Fuchs, Victor, Who Shall Live: Health, Economics and Social Choice (New York 1974), pp. 56–63.
10. The decline of the physician's authority is reflected in the evolution of the doctrine of "informed consent." Initially the patient's right to receive information included only that information which physicians in the same general locality customarily disclosed and in some cases this meant that patients were told little or nothing at all. This ptolemaic view of the consent process has eroded and today in most states a physician must disclose that information which a reasonable patient would consider relevant in deciding whether or not to undergo a course of treatment. Unfortunately, many physicians perceive "informed consent" as but another legal doctrine imposed on them arbitrarily by the courts. Yet by pressing informed consent as a right, patients are really reacting against the dehumanizing trends of modern medicine and are saying to physicians: climb down off your pedestals and treat us with dignity and respect, treat us as human beings. See Macdonald, Michael G. and

Meyer, Kathryn C., "Informed Consent", The Mount Sinai Journal of Medicine, Vol. 43, No. 1 (January-February 1976).

11. Arthur D. Little has estimated that in 10 years Americans will spend $100 billion a year more for health care than the current annual expenditures of 140 billion. American Medical News (May 9, 1977), p.1.
12. Comptroller's Report, pp. 9, 12.
13. *Ibid.*, pp. 6-7.
14. There is almost universal agreement that all who need health care should have access to the system and this is reflected in virtually all proposals for national health insurance. See generally, Davis, Karen, National Health Insurance: Benefits, Costs and Consequences (The Brookings Institution, Washington, D.C. 1975).
15. See generally, Berry, *op. cit.*, p. 110 et seq.; Fuchs, *op. cit.*, pp. 94-95.
16. In addition to the maze of reimbursement regulations, health care institutions are heavily regulated in virtually all other phases of their operations making it the most highly regulated industry in the country. In New York, for example, hospitals are regulated by no less than 96 state agencies, 40 federal agencies, 18 city and county agencies and 10 voluntary and quasi public agencies. For the most part, this regulation is piecemeal and uncoordinated. See Hospital Association of the State of New York, Report of the Task Force on Regulation (New York 1976), p. 8. Do these regulations reflect a concern with quality patient care? In New York, there were two accountants, three attorneys and 69 physicians in selected positions in the New York State Department of Health in 1965; in 1976, there were 170 accountants, 30 attorneys and 60 physicians. These data speak for themselves. Hospital Association of the State of New York, *op. cit. supra*, p. 6. And see, Phillips, Donald F. and Sprague, Joseph E., "Hospital Regulations Reach a Collective Critical Mass", Hospitals, Vol. 50 (July 16 and August 1, 1976).
17. Fuchs, *op. cit.*, p. 54.
18. Thomas, *op. cit., supra*.
19. See, *e.g.*, Havighurst, Clark, "Controlling Health Care Costs: Strengthening the Private Sector's Hand", Journal of Health Politics, Policy and Law, Vol. 1, No. 4 (Winter 1977).
20. Per diem measurements often exaggerate the costs of hospitalization. Increasing lengths of stay are similarly misleading. Rather than prove hospital inefficiency, an increasing length of stay and rising per diem expenses could mean that only the most seriously ill are being hospitalized and that the short stay, relatively inexpensive patient is being treated on an ambulatory basis. The key ingredient which must be included in any analysis of costs is the per capita hospital admission rate. Significantly, the costs of hospitals in New York, which appear high when measured by looking only at per diem expenses and average lengths of stay, compare very favorably to national norms when per capita admissions, which are lower in New York than elsewhere, are taken into account. This is not to minimize the problem of rising health care costs, but rather to show that a more balanced perspective must be brought to bear on the problem.
21. See, Orsini, Louis A., "The Case for Rates Prospectively Determined by State Agencies for All Patients", Viewpoint (January 1974).

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 5, September-October, 1977
Printed in U.S.A.

The Cancer Breakthrough Myth

JAMES F. HOLLAND, M.D.

Introduction

Cancer research, like other magnificent areas of human endeavor, is a broad multifaceted endeavor without definable limits. The term "breakthrough" connotes a military term for a penetration of the enemy's lines and an opportunity to cause the entire front to crumble. It is a term equally applicable to some fragile barrier such as an eggshell, tissue paper, or glass. Breakthrough is a one-time event which shatters the resistance. Breakthroughs of this kind will not occur in cancer research.

Cancer Biology

Cancer is a generic term for a variant manifestation of life. The exquisite organization of living cells evokes amazement akin to viewing the mysterious depths of the heavens. Cells which are adapted to specialized functions, serving one another for preservation of the organism and its very existence, represent the adaptation to multicellular evolution come about over hundreds of millions of years. The specialized functions of cells include preprogramming for death. Some cells survive but a few days, and are part of intricate systems which regulate their own replacement. Other cells are a one-time endowment that mature with the individual and are not replaced as they become senescent and die within the body. Spared from intercurrent disease or accident, it is the death of irreplaceable cells that leads to the death of the organism in ripe old age appropriate for a particular species.

Cancer cells are imperfectly programmed to die. Indeed many other body systems grow more rapidly than cancer cells but have a metabolic destiny to mature along classic lines, eventually reaching a nongrowing state. Brain cells or muscle cells, for example, rapidly grow during embryonic development, but eventually reach a static plateau. Other normal cells are eliminated or die, such as mucosal cells or blood granulocytes. Cancer cells do not mature normally. A disproportionate percentage of cells have the capacity to reproduce and do so, leading to an accumulation of cancer cells which become the mass of cancer tissue.

All aberrant cells do not become cancers. Indeed, something well in excess of two hundred billion cells are formed in the body every day—more than a million cells per second—and some of these are imperfect. A few aneuploid karyotypes of individual cells are frequently seen in normal bone marrow

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From the Department of Neoplastic Diseases, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Requests for reprints should be sent to: James F. Holland, M.D., Chairman, Department of Neoplastic Diseases, Mount Sinai School of Medicine, Fifth Avenue and 100 Street, New York, N.Y. 10029.

preparations. Such aberrant chromosomal patterns in cells most probably are a lethal mutation. The cells are nonviable, either intrinsically, or under the competitive pressure from scavenging cells of the host which attack the surfaces of cells not recognized to be "self." Indeed successful cancer cells are not sufficiently aberrant to be nonviable; and not sufficiently foreign to the host to elicit a response which is effective in totally eliminating the new cellular species.

Immunology

Considerable evidence exists that in addition to grossly aberrant cells which are nonviable, cells with the capacity to become cancers appear with regularity. They are eliminated or controlled by the host so that they never become clinical cancers. Such conclusions derive from the disproportionately high number of neuroblastomas seen in stillborns and in infants dying of other diseases compared to the lower clinical frequency of neuroblastoma. Similar data are true for carcinoma in situ of the prostate, lobular carcinoma of the breast, and carcinoma in situ of the cervix, all of which are incipient neoplastic stages unmatched by an equal frequency of the clinical disease. The interplay of the hosts' impact on tumor cells is a major area of cancer research still to be explored in its fullest reaches. Indeed, spontaneous regressions of established cancers have been recorded, and albeit rare, they demonstrate that the possibility exists. At least one explanation for these phenomena is the concept of cellular surveillance. Lymphocytes processed through the thymus take on new characteristics and are called T cells. They are implicated in cell-to-cell interaction and the secretion of molecules which are active only over a short distance, the lymphokines, some of which have the ability to kill cells. B-lymphocytes and their derivative plasma cells synthesize specific antibodies which together with complement may lead to death of tumor cells. Monocytes which transform to macrophages may specifically recognize tumor cells and kill them. Thus, several reinforcing mechanisms with varying degrees of specificity constitute recognizable host defenses against tumor invasion. This immune defense can be stimulated by nonspecific and specific means as a form of immunotherapy.

Spontaneous regressions of tumors have been reported following bacterial diseases, notably erysipelas and staphylococcal infections. Experimental infection with an attenuated strain of tuberculosis (Bacillus Calmette-Guerin, BCG) has stimulated the rejection of transplanted tumors and the partial control of spontaneous tumor growth. After chemotherapy had reduced the tumor burden substantially, immunization of children with acute lymphocytic leukemia by BCG and irradiated leukemic cells evoked a major response in one-third of children: They are still in remission more than ten years later (1). Additional results with BCG in malignant melanoma, with C. parvum in a variety of metastatic carcinomas, and with levamisole in breast cancer and lung cancer confirm the activity of a broad spectrum of immunologic stimulants. The methanol extraction residue (MER) of BCG is a partial purification product and it too is under vigorous study with suggested benefits.

A highly specific approach to immunotherapy is that which we have reported using tumor cells treated with the neuramindase from Vibrio cholerae (2). In challenge experiments such cells are one thousand times more potent than x-irradiated cells and ten thousand times more effective than formalin-inactivated cells. They can be used after chemotherapy in the treatment of transplanted tumors and of autochthonous neoplasms. In acute myelocytic leukemia, of man, the use of allogeneic neuraminidase-treated myeloblasts has produced exceptionally long remission durations (3).

Tumors are known to secrete abnormal, or abnormal quantities of, biologically active substances into the blood stream. Some of these, as yet imperfectly identified, are known to depress the host's immune response. Immunotherapy may counteract this depression. Some recent experiments suggest that a material leading to immunosuppression is circulating in the plasma and that removal of plasma with substitution by normal plasma has clinical benefits.

Immunologic response to tumors has been of interest for more than a hundred years, dating at least from the first transplantation of a tumor in a Russian horse more than 100 years ago. New understanding of cellular functions, new experimental methods and new drugs all bode well for immunologic approaches to cancer in man. This is a continuing effort in a broad field against our ignorance of the ways of nature. Sallies forward will produce advances, but not breakthroughs.

Chemotherapy

Chemotherapy of cancer is the use of drugs in an attempt selectively to kill tumor cells. Founded as a science by Paul Ehrlich before the turn of the century, chemotherapy of bacterial infections has led to some of the most dramatic pages of medical history. Chemotherapy of cancer is far more difficult, insofar as the similarities between the target cell and the host's normal tissues are much closer than for bacteria. In the 1940s, the modern era of cancer chemotherapy began with the discovery of nitrogen mustard, a derivative of a war gas, and of aminopterin, the fruit of intellectual efforts to make a competitor for the vitamin folic acid. Both drugs are still used today, along with approximately 50 others with specific indications for use in particular types of the hundreds of kinds of cancers. Individual tissues give rise to particular tumor types which may have superficial resemblances from organ to organ but also unique characteristics. There is virtually no organ which does not have at least half a dozen types of cancer—tumors of different appearance and different levels of maturity arising from the several cell types which may be represented in each organ. Tumor cells grow in the aggregate, some cells are dying, some are multiplying, some are in a temporary nongrowing state, and some are maturing (often beyond the state of further reproduction). The most vulnerable target for critical injury from drug therapy is the multiplying pool of cells. They are in the process of vigorous synthesis of new DNA and RNA to make further cellular substance. Interruption of DNA biosynthesis or RNA biosynthesis is a critical lesion that can produce lethal consequences to individual cells. After the death of a portion of the growing pool, cells in the nongrowing pool may again be recruited into reproductive cycle. Repetitive doses of chemotherapy, at varying intervals depending upon the drug and the tumor are therefore usually necessary (4).

One aspect of the great versatility of chemotherapy is the fact that drugs are not regionally confined; they distribute where the blood circulates. To be sure, subtle factors influence drug uptake; the half life of the drug in biologic fluids may be shorter than the time necessary to traverse the capillary wall, the interstitial fluid, the tumor cell membrane, and the various intracellular compartments, to arrive at the specific target site in the cell.

The circulation of blood to tumors is not identical to the circulation of blood to normal body organs. A circumferential circulation often gives a rich blood supply to the cortex of tumors, with a profound deficiency in the center. This is most easily measured by the virtual absence of oxygen in the center of tumors. Indeed, if oxygen cannot get to tumor cells, neither can drug, and those tumor cells are not then growing in any event. The relatively lesser effect of radiotherapy (which depends upon oxygenated cells) and of chemotherapy on very large tumors is a derivative, in part, of this ineffective circulation to the tumor cells. Conversely, small tumor masses of only a few million tumor cells ordinarily have much better circulation (and thus delivery of drug) to each tumor cell. Such micrometastases are better targets for drug therapy, and the opportunity to achieve total eradication is greatly improved.

Although chemotherapeutic practice began as a palliative approach for tumors that were widely disseminated and unsuited for surgical excision or radiotherapeutic destruction, it has been possible in the past 30 years to achieve cures of patients. This fact is of enormous heuristic significance. Choriocarcinoma is a highly lethal neoplasm of the placenta that can be cured by chemotherapy. Indeed, chemotherapy is the treatment of choice for this disease, superseding even surgery. In acute leukemia of childhood, where surgery is never suitable because the disease is disseminated from the onset in the blood-forming tissues, chemotherapy with combinations of drugs, tightly scheduled, may be curative in approximately half the cases (5). Chemotherapeutic eradication has also been achieved in an appreciable proportion of patients with Hodgkin's disease, diffuse large cell (histiocytic, reticulum) lymphoma, and certain testicular cancers.

Adjuvant Chemotherapy

The use of chemotherapy with surgery has provided a major mechanism that decreases the bulk of tumor in the primary operable site while reducing or eradicating micrometastatic disease. Such micrometastases may readily be inferred, by the natural behavior of tumors, to be the site of recurrence after the primary tumor is removed. In some staging procedures, such as defining the number of axillary lymph nodes involved with breast cancer, the prediction of natural history is highly accurate. In women with four nodes or more involved with metastatic breast cancer, the relapse rate approaches 90 percent, a clear indication that clinically undetectable residual disease was present in disseminated form (6). Multiple studies in breast cancer have demonstrated unambiguous evidence of beneficial chemotherapeutic effect on operated patients at high risk of relapse. These data include transforming breast cancer with four or more nodes involved from a certain recurrence rate of 90 percent, with death in 60 percent by eight years, to a 70 percent survival without evidence of disease at eight years (7). The question in the adjuvant chemotherapy of breast cancer is how to optimize a proved advance. This finding, too, is not a breakthrough but the result of complex research design, hard work, and the time-honored technique of standing on the accomplishments of our predecessors, the better to reach new heights. The success is not unexpected, but rather the culmination of 15 years of work in chemotherapy of advanced breast cancer and surgical adjuvant therapy of breast cancer.

In addition to the success of surgical adjuvant chemotherapy in breast cancer, a similar phenomenon has occurred in osteogenic sarcoma in which each of two chemotherapies, adriamycin (8) and the combination of vincristine, methotrexate, and citrovorum factor (9), have proved successful. The fact that adjuvant chemotherapy is not specifically dependent on a particular drug regimen validates the principle involved. The improved success with chemotherapy of disseminated osteosarcoma has allowed the investigational combination of surgery and chemotherapy in limb-sparing operations. The tumor, markedly devitalized by chemotherapy or by chemotherapy and radiotherapy, is removed and replaced by a bone or a prosthetic device, leaving the limb physiologically compromised but nonetheless intact without amputation.

A broad area of combination surgery and chemotherapy can be foreseen, using drugs of known activity for specific tumor types of particular organs. It is clear, however, that drugs shown to be inactive for advanced cancers with large nongrowing populations may exert activity on micrometastatic deposits with a large growth fraction. It is also manifest that tumors treated in such fashion are clinically undetectable. Thus, the results of therapy must be judged by different parameters from those ordinarily used. One parameter would be the comparison of outcome with a group of patients similarly treated save for a single feature—chemotherapy, for example. Another way would be to follow the behavior of tumors too small to be recognized by physical examination or radiologic detection by monitoring the secretion of unique substances detectable in the blood plasma. Such characteristic molecules are many, and although not absolutely specific for particular tumors, give good biochemical indication of tumor presence which correlates with tumor behavior. Unfortunately, none of the biochemical monitoring tests are sufficiently characteristic of common tumors to serve as a screening device. Indeed, considerable optimism still resides in the possibility of finding specific biochemical tests for early cancer which could be incorporated into screening examinations.

In addition to surgical adjuvant chemotherapy, surgical adjuvant immunotherapy has also emerged as an area of legitimate investigation. Host-mediated destruction of tumor is more effective against smaller rather than larger tumors. The same concepts that allow for the stimulation of a host's defenses against micrometastatic tumor after chemotherapeutic destruction are relevant following surgical excision alone or after radiotherapeutic destruction.

Radiotherapy

The quality of radiotherapy has improved in the last decade with the development of superior instruments for delivering high energy beams. Linear accelerators have desirable characteristics of beam collimation, energy, and field accuracy that make for improved radiotherapy. Particle irradiation is under active investigation. Neutron irradiation is much less dependent on oxygenation of target tissues, and thus may have effects superior to x-rays or gamma rays on large tumors. Pi meson irradiation has shown desirable characteristics of delivery to specific depths of tissue, thus concentrating the effect around the actual tumor volume. Although neither neutrons nor pi mesons are widely available, their potential could make them reliable in the next decade should the early investigations prove fruitful.

Diagnosis

Diagnostic methodology with new approaches to direct visualization of much of the gastrointestinal tract including the esophagus, stomach, duodenum, rectum, and the colon, supplement by a major amount the visualization that can be achieved by contrast radiography. Access to duodenal orifices also permits retrograde cholangiography and pancreatography. The contribution of fiberoptic light transmission to this new generation of endoscopic instruments has been critical.

Noninvasive techniques of visualization have also improved markedly. Ultrasonography, the reflection of sound waves off anatomical structures, has provided a new tool for definition of anatomy, particularly within the abdominal cavity. Ovarian masses, pancreatic masses, and retroperitoneal masses often can be visualized with confidence.

A most dramatic achievement has been the discovery of computerized axial tomography, the ability to make truly accurate cross-sectional pictures of the body. Distortions in the anatomy of the pancreas, the adrenals, retroperitoneal lymph nodes, the prostate, gynecologic organs, and the brain have been pinpointed in such a way as to add materially to the diagnostic potential of x-ray in these areas.

Etiology

Lastly (or firstly), the etiology of cancer has become somewhat clarified as recognition of specific chemical substances or mixtures of substances have been implicated in the causation of certain cancers. The role of cigarette smoke as the most pernicious correctible health factor with respect to cancer and heart disease has been stressed. Its recognition, however, has barely changed social custom. The delineation of mesothelioma as a tumor highly correlated with asbestos exposure provides another challenge because of the very large number of individuals who already have been exposed occupationally to asbestos. The incidence of this tumor is expected to increase sharply based on exposure that has already occurred. The size of the exposed population provides a basis for study. We have inaugurated a center for mesothelioma research at Mount Sinai. We expect to define, in a prospective way, those factors which appear to correlate with the appearance of subsequent mesothelioma. Such factors as immunologic competence, emotional factors, nutrition and exposure to other environmental stimuli may be relevant in determining who among those exposed develops the cancer.

The appearance of a unique tumor among workers with vinyl chloride, hemangiosarcoma of the liver, alerted the entire nation to the fact that particular chemicals are carcinogens for some exposed persons. How these chemicals work on the molecular biology of the cell, and how society organizes itself to prevent this occupational and societal exposure, are vastly different, yet interrelated, points on the same continuum of inquiry.

The clear causal relation of viruses to a score of animal cancers has not provided unambiguous evidence of the viral etiology of human cancers, although known viruses are associated with two. It is not clear whether viruses present in human tumors are there as a contaminating passenger or as an etiologically causative agent. Since some tumors in animals, analogous to certain human neoplasms, are known to be caused by viruses, the possibility that some human cancers may also be viral in origin has not been excluded. Footprints of viruses, in biochemical terms, are abundantly available, but this is not conclusive proof (10). Any viruses that might be discovered would not have the same infectious capacities as those of common epidemic diseases. This appears axiomatic since epidemics of cancer do not occur in the same fashion as the common viral diseases. Indeed, it may be that viruses commonly associated with benign, simple diseases inflict a sublethal injury on some cells. On rare occasions, instead of killing target cells, the cellular injury, if not repaired, would transform them into cancer cells. Thus, the biologic concept of cancer cells as nonlethal aberrancies from normal cells comes full circle.

Conclusion

None of the multitude of accomplishments contributing to the advances described fit the definition of a breakthrough. Rather a broad advance of an entire front with progress in immunology, chemotherapy, surgery, radiology, diagnosis, chemical carcinogenesis, and viral oncology has occurred. A major advance in any one would still constitute a sally into the unknown. When dealing with hundreds of diseases, broad areas of information still to be discovered, major unknowns still to be tested systematically and applied to man, ethical requirements of appropriate medical and humanistic conduct in the carrying out of these investigations, and the factors of time, trained personnel, equipment, supplies, and other required resources, it seems to this observer, that breakthroughs are unlikely. Rather, steady accelerating advance and increasing cures of more kinds of cancer appear likely, with an increasing appreciation by society that cancer research is indeed progressing towards what society wants: prevention of cancer; failing that, cure of cancer in increasingly higher percentages; and failing that, improvement in the treatments available which extend life of high quality and which decrease suffering.

References

1. Mathé, G.: Immunotherapy of Acute Lymphocytic Leukemia. Ten Year Follow Up. In *Adjuvant Therapy of Cancer*. Eds. Salmon, S.E. and Jones, S.E. Elvesier, North-Holland, Amsterdam (In press 1977).
2. Bekesi, J. G., Roboz, J. P., and Holland, J. F.: Immunotherapy with Neuraminidase-Treated Murine Leukemia Cells after Cytoreductive Therapy in Leukemia Mice in Modulation of Host Immune Resistance in the Prevention or Treatment of Induced Neoplasms, Fogarty International Center Proceedings No. 28, DHEW, No (NIH) 77-823, pp. 219-234, 1977.
3. Holland, J. F. and Bekesi, J. G.: Immunotherapy of Human Leukemia with Neuraminidase-Modified Cells, Symposium on Immunotherapy in Malignant Diseases, Med Clin North Am 60:539-49, 1976.
4. Holland, J. F. and Frei, E. III, eds. *Cancer Medicine,* Lea and Febiger, Philadelphia 1973.
5. Holland, J. F. and Glidewell, O. J.: Oncologists' Reply: Survival Expectancy in Acute Lymphocytic Leukemia, New Engl J Med 287:769-777, 1972.
6. Fisher, B., Slock, N., Katryck, et al. Ten-Year Follow-Up Results of Patients with Carcinoma of the Breast in a Cooperative Clinical Trial Evaluating Surgical Adjuvant Chemotherapy, Surg Gyn Obstet 140:528-534, 1975.
7. Cooper, R. G., Holland, J. F., and Glidewell, O.: Breast Cancer: Surgery and Chemotherapy (Submitted for publication, 1977).
8. Cortes, E. P., Holland, J. F., Wang, J. J., Sinks, L. F., Blom, J., Senn, H., Bank, A., and Glidewell, O. J.: Amputation and Adriamycin in Primary Osteosarcoma, New Engl J Med 291:998-1000 (Nov.) 1974.
9. Jaffe, N., Frei, E. III, Traggis, D., and Bishop, Y.: Adjuvant Methotrexate and Citrovorum—Factor Treatment of Osteogenic Sarcoma, New Engl J Med 291:994-997, 1974.
10. Baxt, W., Yates, J. W., Wallace, H. J., and Spiegelman, S.: A Study of Leukemia-Specific DNA Sequences in the White Blood Cells of Identical Twins, Proc Nat Acad Sci 70:2629-2632, 1973.

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Acknowledgment

The late Rafael Navarro was an international publisher. At the young age of 39 years he came under my care with a severe respiratory disorder. At the time I was just leaving London to attend the Siltzbach World Sarcoidosis Congress in New York City. When I told him I was going there he decided to come with me. This did not seem a bad idea since a large number of international chest physicians were about to meet there at the time. When he arrived in New York, we admitted him to The Mount Sinai Hospital where he was looked after by Louis Siltzbach and his team and also treated by James Holland and his team. He never did come back to England. From New York City he went down to Miami where he was surrounded by a loving family and found sanctuary in his beloved Catholic church. He was under the close medical supervision of Dr. Nathan Segel.

Rafael Navarro very much would have enjoyed reading the Siltzbach Festschrift since several of the contributors had looked after him and he got to know each of his medical attendants very well. Although he did not live to see and handle this book, his generous nature made it possible.

D Geraint James

D. GERAINT JAMES,
Guest Editor

The Mount Sinai Journal of Medicine

Volume 44, Number 6, November-December 1977

SARCOIDOSIS AND RESPIRATORY DISORDERS:

Festschrift in Honor of Louis E. Siltzbach, M.D.

D. GERAINT JAMES, M.D., Guest Editor

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Curriculum Vitae: Louis E. Siltzbach

Louis E. Siltzbach, M.D. Born May 27, 1906 U.S.A.

Education

Townsend Harris Hall 1919–1922
City University of New York 1922–1923
Columbia University 1923–1925
Long Island College of Medicine (Downstate College of Medicine) 1929 M.D.
Internship: Lebanon Hospital, New York 1929–1931
Assistant Resident: Montefiore Hospital 1931–1932

Training

University of Vienna August 1932-December 1933
Research Fellow in Pathology–Professor J. Erdheim
in Bacteriology–Professor E. Lowenstein
in Radiology–Dr. Felix Fleischner
Montefiore Hospital: Research Fellowship, Pulmonary Diseases 1934–1937
Chiefs–Dr. Harry Wessler and Dr. Max Pinner
Nathan Hofheimer Foundation Grant 1941–1943–Research: Prognosis–Pulmonary Tuberculosis

Hospital Appointments

Mount Sinai Hospital, New York
- Adjunct Physician–Thoracic Diseases, 1942–1946
- Adjunct Physician–Department of Medicine, 1946–1953
- Founder and Chief, Sarcoidosis Clinic, 1946–1974
- Associate Physician–Department of Medicine, 1953–1960
- Attending Physician and Director of Thoracic Diseases Division, 1960–1974
- Consultant for Thoracic Diseases, Department of Medicine, 1974– to date

Montefiore Hospital, New York
- Adjunct Physician, Division Pulmonary Diseases, 1934–1938
- Associate Physician, Division Pulmonary Diseases, 1938–1947
- Attending Physician, Division Pulmonary Diseases, 1947– to date

Other Hospital and Clinic Appointments

Consultant, Pulmonary Diseases, Lebanon Hospital, 1957–1970
Visiting Associate Physician, Rockefeller University Hospital, 1959–1966
Guest Investigator, Rockefeller University, in Laboratories of Dr. M. W. Chase, Dr. J. G. Hirsch, and Dr. Z. A. Cohn
Consultant, Rockefeller University Hospital, 1966– to date
Consultant, Pulmonary Section, Kingsbridge Veterans Hospital, New York, 1974– to date
Physician in Charge, Chest Consultation Service, N.Y.C. Bureau of T.B., 1934–1942
Chief Medical Consultant, Altro Health and Rehabilitation Service, 1935– to date

Diplomate American Board of Internal Medicine–1940

Teaching Appointments

Assistant Clinical Professor of Medicine, Columbia College of Physicians and Surgeons 1947–1957
Associate Clinical Professor of Medicine, Columbia College of Physicians and Surgeons 1957–1966
Clinical Professor of Medicine, Mount Sinai School of Medicine, 1966–1974
Clinical Professor of Medicine, Emeritus, Mount Sinai School of Medicine, 1974–to date
Guest Professor and/or Invited Lecturer:
Oxford University, Royal Free Hospital (London), University of Kyoto (Japan), University Rio de Janeiro, University Monte Video, Hadassah University, University of Zurich, University of Paris, All India Institute of Medical Sciences, Charles IV University (Prague).

Schools of Medicine: Harvard University, University of Cincinnati, University of Buffalo, Georgetown University, George Washington University, Cornell University, Downstate Medical Center, New York University, University of Washington, Mayo Clinic, Howard University, University of California, (San Francisco), Boston University, State University at Stoneybrook, University of Rochester, and others.

Other Educational and Research Activities

Executive Secretary, International Committee on Sarcoidosis, 1966- to date
Director of International Kveim testing program in 38 countries, 1960–1966
Opening speaker and organizer, 1st International Conference on Sarcoidosis, London, 1958
Opening speaker and organizer, 4th International Conference on Sarcoidosis, Paris, 1966
Opening speaker and organizer, 5th International Conference on Sarcoidosis, Prague, 1969
Chairman and organizer, 7th International Conference on Sarcoidosis, New York Academy of Sciences, New York, 1975
Organizer, 8th (forthcoming) International Conference on Sarcoidosis, Cardiff, 1978
Blankehorn Memorial Lecturer (University of Cincinnati) 1970
John Mason Tyler Lecturer, Massachusetts Thoracic Society, 1974
Principal reporter on Epidemiology of Sarcoidosis, International Union against Tuberculosis, Rome, 1963
Member Task Force on Research on Respiratory Diseases, National Heart and Lung Institute, 1972
Member, Ad Hoc Study Section, National Institute of Allergy and Infectious Diseases, 1973
Consultant to the Tuberculosis Research Unit and the Biological Standards Laboratory, Medical Research Council, Great Britain, 1963–1969
Organizer, moderator, and participant in Symposia on Granulomatous Disorders at meetings of the American Thoracic Society, and the Trudeau Society; in Denver, Boston, Philadelphia, San Francisco, New York, Seattle, Cincinnati, Cleveland, Rochester, Buffalo, Ottawa; The American College Chest Physicians; in London, Rome, Nice, Copenhagen, Tokyo, Kyoto, Milan, Lausanne, Geneva, Mexico City, Jerusalem and Tel Aviv, Montreal, Toronto, Washington, D.C., Seattle, New York; British and French Thoracic Society in Paris, London, San Francisco.

Grants and Contracts

National Institutes of Health Research Grant, "Fractionation of Kveim Tissue Suspensions", 1958- to date
National Heart and Lung Institute Contract, "*In Vitro* test for Sarcoidosis," 1974- to date

Honors and Awards

AOA Alumni Award, Downstate Medical College, 1975
AOA Faculty Award, Mount Sinai School of Medicine, 1976
Jacobi Medallion, Alumni Association, Mount Sinai School of Medicine, 1976
Issue of Archivio Monaldi (Naples) Jan.-Feb. 1976. Dedicated to D. G. James and L. E. Siltzbach

Memberships

New York Academy of Medicine
New York Academy of Sciences
Harvey Society
American Thoracic Society
Honorary Fellow, National Academy of Medicine, Brazil
Honorary Fellow, 1st Asian College of Chest Physicians Conference, Kyoto, Japan
Honorary Fellow, International Forlanini Association, Rome, Italy
Royal Society of Medicine (London) (Associate)
Fellow, American College Chest Physicians
American Association for the Advancement of Science
New York Trudeau Society
Archeological Institute of America

Bibliography: **Louis E. Siltzbach**

1. Siltzbach, L. E.: *The significance of repeated red-cell sedimentation determinations in pulmonary tuberculosis*. Am. Rev. Tuberc. 29:673, 1934.
2. Siltzbach, L. E.: *Ueber die linksseitige totale kavernenlunge*. Virchows Archiv. 292:652, 1934.
3. Siltzbach, L. E.: *The silicosis hazard in mechanical dentistry* (With the technical assistance of Jack Siegel). JAMA 113:1116, 1939.
4. Siltzbach, L. E. and Nayer, H. R.: *Woldman's phenolphthalein test in intestinal tuberculosis*. Am. J. Digestive Dis. 7:519, 1940.
5. Siltzbach, L. E.: *Rehabilitation of the tuberculous*. Am. Rev. Tuberc. 44:357, 1941.
6. Siltzbach, L. E.: *Medical aspects of the rehabilitation of the tuberculous*. The experience of a quarter century with 964 patients at Altro Work Shops. Am. Rev. Tuberc. 46:489, 1942.
7. Siltzbach, L. E.: *The sheltered workshop in the rehabilitation of the tuberculous*. Medical experience at Altro 1915–1939, Milbank Memorial Fund Quarterly 21:80, 1943.
8. Siltzbach, L. E.: *Clinical evaluation of the rehabilitation of the tuberculous*. Experience at Altro Work Shops 1915–1939 (*Monograph*). Natl. Tuberc. Assoc. 1944.
9. Siltzbach, L. E.: *Penicillin therapy in a case of chronic suppurative bronchiectasis*. J. of Mt. Sinai Hosp. 12:825, 1945.
10. Siltzbach, L. E.: *Carcinoma simulating pulmonary tuberculosis*. Differential diagnosis in the presymptomatic stage in two cases. Am. Rev. Tuberc. 55:170, 1947.
11. Siltzbach, L. E.: *Intratracheal penicillin therapy in suppurtive bronchiectasis*. Arch. of Internal Med. 79:570, 1947.
12. Siltzbach, L. E., Posner, Aldoph and Medine, Myer M.: *Cortisone therapy in sarcoidosis*. Effect in a case with virtual blindness, JAMA 147:927, 1951.
13. Siltzbach, L. E.: *Effects of cortisone in sarcoidosis*. A study of thirteen patients. Am. J. of Med. 12:139, 1952.
14. Siltzbach, L. E. and Som, Max L.: *Sarcoidosis with bronchial involvement*. A report of two cases with bronchoscopic biopsies. J. of Mt. Sinai Hosp. 19:473, 1952.
15. Siltzbach, Louis E. and Ehrlich, Joseph C.: *The Nickerson-Kveim Reaction in Sarcoidosis*. Am. J. Med. 16:790, 1954.
16. Siltzbach, L. E.: *Pulmonary sarcoidosis*. Am. J. of Surg. 89:556, 1955.
17. Altchek, Albert, Gaines, Joseph A. and Siltzbach, Louis E.: *Sarcoidosis of the uterus*. Am. J. of Obstetrics and Gynecology 70:540, 1955.
18. Siltzbach, L. E.: *Relapse and rehabilitation in the era of antituberculosis drugs*. J. of Mt. Sinai Hosp. 23:628, 1956.
19. Siltzbach, L. E.: *Progress in sarcoidosis*—Editorial. Am. J. Med. 22:841, 1957.
20. Siltzbach, L. E.: *The aetiology of sarcoidosis*. Postgraduate Med. J. 34:254, 1958.
21. Siltzbach, L. E.: *Clinical conference on sarcoidosis*. J. of Mt. Sinai Hosp. 25:548, 1958.
22. Siltzbach, L. E., Imberman, Mark M., Grossman, Howard: *Prednisone and prednisolone therapy*. Am. Rev. Resp. Dis. 78:305, 1958 (abstract).
23. Siltzbach, L. E.: *Sarcoidosis in Pregnancy*. Gutmacher, Alan F. and Rovinsky, Joseph J.: Surgical Complications of Pregnancy. Waverly Press (Baltimore) 137, 1960 (Chapter).
24. Siltzbach, L. E.: *Sarcoidosis—prevalence and diagnosis*. Merck Sharp & Dohme Seminar International 9:2, 1960.
25. Siltzbach, L. E.: *Sarcoidosis: Frequencia y diagnostico*. El Torax, Montevideo, Uruguay 9:155, 1960.
26. Siltzbach, L. E.: *The Kveim test in sarcoidosis—A study in 750 patients*. JAMA 178:476, 1961.
27. Siltzbach, L. E.: *Chronic lung disease*. Proc. of Royal Soc. of Med. 54:975, 1961.
28. Teirstein, Alvin S., Wolf, Bernard S. and Siltzbach, Louis E.: *Sarcoidosis of the skull*. New Engl. J. Med. 265:65, 1961.
29. Siltzbach, L. E.: Sarcoidose (Prevalencia e diagnostico) Merck Sharp & Dohme Internatl., *Compendio Medico* (Portuguesa) 89:6, 1961.
30. Hirsch, James G., Cohn, Zanvil A., Morse, Stephen I., Schaedler, Russell W., Siltzbach, Louis E., Ellis, John T., and Chase, Merrill W.: *Evaluation of the Kveim reaction as a diagnostic test for sarcoidosis*. New Engl. J. Med. 265:827, 1961.

31. Siltzbach, L. E.: *Sarcoidosis: Prevalencia y diagnostico.* Merck Sharp & Dohme Internatl., Compendio Medico (Spanish) Vol 30 #89 page 3, 1961.

32. Siltzbach, L. E.: *The Kveim test in sarcoidosis—Editorial.* Am. J. Med. 30:495, 1961.

33. Siltzbach, L. E.: *Current status of the Nickerson-Kveim reaction.* Am. Rev. of Respir. Dis. 84:89, 1961.

34. Siltzbach, L. E.: *The Kveim test in sarcoidosis and tuberculosis.* Excerpta Medica. Internatl. Congr. Ser. 44:587, 1961 (abstract).

35. Chase, M. W. and Siltzbach, L. E.: *Further studies in fractionation of materials used in the intracutaneous diagnostic test for sarcoidosis.* Excerpta Medica. Internatl. Congr. Ser. 42:58, 1961.

36. Siltzbach, L. E.: *Ancillary techniques in the investigation of chronic lung diseases.* J. of Mt. Sinai Hosp. 29:395, 1962.

37. Gottlieb, Arlan J., Teirstein, Alvin S., Siltzbach, L. E.: *Idiopathic diffuse interstitial pulmonary fibrosis.* Am. Rev. Resp. Dis. 86:110, 1962 (abstract).

38. Friedman, Oscar H. Blaugrund, Stanley M. and Siltzbach, L. E.: *Biopsy of the bronchial wall as an aid in diagnosis of sarcoidosis.* JAMA 183:646, 1963.

39. Siltzbach, L. E.: *Bronchial wall biopsy in sarcoidosis—Editorial.* JAMA 183:683, 1963.

40. Anderson, R., Brett, G. Z., James D. Geraint and Siltzbach, L. E.: *Prevalence of intrathoracic sarcoidosis.* Medicina Thoracalis 20:152, 1963.

41. Siltzbach, Louis E. and Blaugrund, Stanley M.: *Sarcoidosis of the mucosa of the respiratory tract.* Annals of Otology, Rhinology and Laryngology 72:923, 1963.

42. Siltzbach, L. E.: *Diffuse pulmonary granulomatoses and fibroses.* Modern Treatment (Harper and Row) 1: 1964 (Chapter). See also, *Granulomatosi e fibrosi polmonari diffuse.* Terania Moderna. Il Pensiero Scientifico Editore, Rome. (Chapter 64–81) Vol. 1, Number 2 Sept 1965. Carl Muschenheim, Editor.

43. Siltzbach, L. E.: *The Kveim test in tuberculosis, beryllium disease, leprosy and sarcoidosis.* Am. Rev. Resp. Dis. 90:308, 1964 (abstract).

44. Siltzbach, L. E.: *An international Kveim test study.* Acta Med. Scand. Suppl. 425–176:178, 1964.

45. Siltzbach, L. E.: *Significance and specificity of Kveim reaction.* Acta Med. Scand. Suppl. 425–176:74, 1964.

46. Siltzbach, Louis E. and Cahn, Lester R.: *Random biopsy of bronchial and palatal mucosa in the diagnosis of sarcoidosis.* Acta Med. Scand. Suppl. 425-176:230, 1964.

47. Siltzbach, Louis E., and Teirstein, Alvin S.: *Chloroquine therapy in 43 patients with intrathoracic and cutaneous sarcoidosis.* Acta Med. Scand. Suppl. 425–176:302, 1964.

48. Hirschorn, K., Schreibman, R. R., Bach, F. H., and Siltzbach, L. E.: *In vitro studies of lymphocytes from patients with sarcoidosis and lymphoproliferative diseases.* The Lancet 2:842, 1964.

49. Silverstein, Allen, Feuer, Martin M., and Siltzbach, Louis E.: *Neurologic manifestations of sarcoidosis.* Trans. Am. Neuro. Assoc. 89:257, 1964 (abstract).

50. Silverstein, Allen, Feuer, Martin M., and Siltzbach, Louis E.: *Neurologic sarcoidosis-study of 18 cases.* Archiv. of Neurology 12:1, 1965.

51. Gottlieb, Arlan J., Spiera, Harry, Teirstein, Alvin S., Siltzbach, Louis E.: *Serologic factors in idiopathic diffuse interstitial pulmonary fibrosis.* Am. J. Med. 39:405, 1965.

52. Siltzbach, L. E.: *Current thoughts on epidemiology and etiology of sarcoidosis—Editorial.* Am. J. Med. 39:361, 1965.

53. Siltzbach, L. E.: *Geographic Aspects of Sarcoidosis.* Trans. of N.Y. Acad. of Sciences, Series II, Vol. 29, No. 4, pp 364–374, Feb. 1967.

54. Siltzbach, L. E.: *Sarcoidosis: Clinical Features and Management.* Med. Clinics of No. Amer. 51:483, 1967 (pp 483–501).

55. Present, Daniel H. and Siltzbach, Louis E.: *Sarcoidosis among the Chinese and a review of the worldwide epidemiology of sarcoidosis.* Am. Rev. Resp. Dis. 95:285, 1967 (pp 285–291).

56. Siltzbach, L. E.: *Aspects Cliniques et Experimentaus du Test de Kveim dans la Sarcoidose.* Le Poumon et le Coeur 23:499–527, 1967.

57. Siltzbach, L. E.: *Allocution du Professour L. E. Stiltzbach.* pp 1–3, 1967. La Sarcoidose, Masson et Cie. Paris.

58. Siltzbach, L. E.: *Concepts of Sarcoidosis in the Light of the Kveim Reaction.* pp 129–140, 1967. La Sarcoidose, Masson et Cie. Paris.

59. Cohn, Z. A., Fedorko, M. E., Hirsch, J. G. Morse, S. I. and Siltzbach, L. E.: *The Distribution of Kveim Activity in Subcellular Fractions from Sarcoid Lymph Nodes.* pp 141–149, 1967. La Sarcoidose, Masson et Cie. Paris.

60. Chase, M. W. and L. E. Siltzbach. *Concentration of the Active Principle Responsible for the Kveim Reaction.* pp 150–153, 1967. La Sarcoidose, Masson et Cie. Paris.

61. Mitchell, D. N., Siltzbach, L. E., Sutherland, I. and D'Arcy Hart, P.: *Some Further Observations on the Kveim Test in Relation to B.C.G. Vaccination and Tuberculin Sensitivity.* pp 154–161, 1967. La Sarcoidose, Masson et Cie. Paris.

62. Siltzbach, L. E.: *An International Kveim Test Study* (1960–1966) pp 201–213, 1967. La Sarcoidose, Masson et Cie. Paris.

63. Mandi, L., Kelemen, T. J. and Siltzbach, L. E.: *Signification de la Reaction de Kveim dans le Diagnostic de la Sarcoidose.* pp 229–232, 1967. La Sarcoidose, Masson et Cie. Paris.

64. Siltzbach, L. E.: *Sarcoidosis and Mycobacteria—Editorial.* The Am. Rev. Resp. Dis. 97:1–8, 1968.

65. Siltzbach, L. E. with Ramirez, E. A., Ramirez de Arellano, G.: *Results of testing with Kveim antigen in sarcoidosis suspects in Puerto Rico.* pp 219–223, 1967. La Sarcoidose, Masson et Cie. Paris.

66. Mitchell, D. N., Siltzbach, L. E., Sutherland, I. and Hart, P. D'Arcy: *Sarcoidosis and immunologic deficiencies.* In D. Gergsma (ed.), *Immunologic Deficiency Diseases in Man.* New York: The National Foundation March of Dimes. pp 364–369, 1967.

67. Oreskes, I. and Siltzbach, L. E.: *Changes in rheumatoid factor activity during the course of sarcoidosis.* Am. J. Med. 44:60–67, 1968.

68. Siltzbach, L. E. and Duberstein, J.: *Arthritis in sarcoidosis.* Clin. Orth. and Related Res. 57:31–50, 1968.

69. Siltzbach, L. E.: *The Enigma of Sarcoidosis.* Hospital Practice. pp 80–91, Oct. 1968.

70. Siltzbach, L. E. and Greenberg, G. M.: *Childhood sarcoidosis—A study of 18 cases.* NEJM 279:1239–1245, Dec. 5, 1968.

71. Siltzbach, L. E.: *Editorials—Progressive systemic sclerosis with pulmonary involvement.* Dis. of Chest. Vol 54, #6, pp. 487–488, Dec. 1968.

72. James, D. G., Siltzbach, L. E., Sharma, O. P., Carstairs, L. S.: *A Tale of Two Cities.* Arch. Intern. Med. Vol. 123, pp 187–191, Feb. 1969.

73. Siltzbach, L. E. and Waraich, B. A.: *Effects of Corticosteroid Therapy on Kveim Reactivity in Sarcoidosis.* Am. Rev. Resp. Dis. Vol 99, pp 614–616, April 1969.

74. Spilberg, I., Siltzbach, L. E. and McEwen, C.: *The Arthritis of Sarcoidosis.* Arthritis and Rheumatism. Vol 12, #2, pp 126–137, April 1969.

75. Siltzbach, L. E.: *Etiology of Sarcoidosis.* The PRACTITIONER. 202:613–618, May 1969.

76. Celikoglu, S. I. and Siltzbach, L. E.: *A Study of Sarcoidosis and Leprosy in Turkey employing the Kveim Reaction.* Dis. of the Chest. Vol. 55, #5, pp 400–404, May 1969.

77. Silverstein, A. and Siltzbach, L. E.: *Muscle Involvement in Sarcoidosis.* Arch. Neurol. Vol. 21, pp 235–241, Sept. 1969.

78. Siltzbach, L. E.: *Sarcoidosis—International Forum.* Therapeutic Notes. Vol 74 pp 155–158, Nov.-Dec. 1967.

79. Siltzbach, L. E.: *Sarcoidosis* (Chapter) In Conn and Conn (eds.) Current Diagnosis. pp 935–939, 1968. Saunders and Co.

80. Siltzbach, L. E.: *Sarcoidosis.* The Japanese Journal of Chest Dis. Vol 29, #1, pp 1–4, Jan. 1970.

81. Siltzbach, L. E.: *Sarcoidosis—A Century of Search.* Cincinnati Jour. of Med. 51:187–194, 1970.

82. James, D. Geraint and Siltzbach, Louis E.: *Sarcoidosis.* (Chapter) In S. Maddin (ed.) Current Dermatologic Management. 1st ed., pp 224–226, 1970.

83. Hirshaut, Y., Glade, P., Vieira, L.O.B.D., Ainbender, E., Dvorak, B., and Siltzbach, L. E.: *Sarcoidosis, another disease associated with serologic evidence for Herpes-like virus infection.* N.E.J.M. 283:502–506, 1970.

84. Pearson, J. M. H., Pettit, J. H. S., Siltzbach, L. E., Ridley, D. S., Hart, P. D'Arcy and Rees,

R. J. W.: *The Kveim test in Lepromatous and Tuberculoid Leprosy*. Int. J. of Leprosy, Vol. 37, #4, pp 372–381, 1969.

85. Siltzbach, L. E.: *Opening of Conference,* Vth International Conference on Sarcoidosis. Levinsky, L. and Macholda, F. (eds.) Praha, Universita Karlova, 1971, pp 33–34.

86. Siltzbach, L. E.: *The Kveim-test historical aspects*. Vth International Conference on Sarcoidosis. Levinsky, L. and Macholda, F. (eds.) Praha, Universita Karlova, 1971, pp 66–67.

87. Chusid, E. L., Shah, R., Siltzbach, L. E.: *Tuberculin sensitivity in Sarcoidosis*. Vth International Conference on Sarcoidosis. Levinsky, L. and Macholda, F. (eds.) Praha, Universita Karlova, 1971, pp 139–143.

88. Celikoglu, S., Vieira, L. O. B. D., Siltzbach, L. E.: *Serum Immunoglobulins levels in Sarcoidosis*. Vth International Conference on Sarcoidosis. Levinsky, L., and Macholda, F. (eds.). Praha, Universita Karlova, 1971, pp 168–170.

89. Siltzbach, L. E., Glade, P. R., Hirshaut, Y., Vieira, L. O. B. D., Celikoglu, S. I., Hirschhorn, K.: *In vitro stimulation of peripheral lymphocytes in Sarcoidosis*. Vth International Conference on Sarcoidosis. Levinsky, L. and Macholda, F. (eds.). Praha, Universita Karlova, 1971, pp 217–220.

90. Siltzbach, L., Vieira, L. O. B. D., Waraich, B. A.: *Effects of oral corticosteroids on Kveim reactivity in 30 Kveim positive subjects with sarcoidosis*. Vth International Conference on Sarcoidosis. Levinsky L., and Macholda, F. (eds.). Praha, Universita Karlova, 1971, pp 365–366.

91. Siltzbach, L. E., Ruttenberg, M. A.: *Chemical and physical characteristics of the active principle in Kveim suspensions*. Vth International Conference on Sarcoidosis. Levinsky L., and Macholda, F. (eds.). Praha, Universita Karlova, 1971, pp 371–374.

92. Teirstein, A. S., Siltzbach, L. E., Berger, H. W., and Barthold, D.: *Causes of death in sarcoidosis: the prognostic significance of the presenting chest radiograph*. Vth International Conference on Sarcoidosis. Levinsky, L. and Macholda, F. (eds.). Praha, Universita Karlova, 1971, pp 541–545.

93. Chusid, E. L., Shah, R., and Siltzbach, L. E.: *Tuberculin tests during the course of sarcoidosis in 350 patients*. Am. Rev. of Resp. Dis. 104:13–21, 1971.

94. Siltzbach, L. E.: *Sarcoidosis* (Chapter) IMMUNOLOGICAL DISEASES, 2nd ed., Little, Brown and Co. pp 581–599, 1971.

95. Siltzbach, L. E.: *Sarcoidosis*. Chapter in Cecil-Loeb Textbook of Medicine (Beeson and McDermott) 13th ed., W. B. Saunders Co., Phil. Pa. pp 826–834, 1971.

96. Siltzbach, L. E.: *Diffuse pulmonary granulomatosis and fibrosis: Diagnosis and treatment*. (Banyai and Gordan) Advances in Cardiopulmonary Diseases, Vol IV pp 306–319, 1969.

97. Siltzbach, L. E., Vieira, L. O. B. D., Topilsky, M., and Janowitz, H. D.: *Is there Kevim responsiveness in Crohn's disease?* The Lancet pp 634–636, Sept 18, 1971.

98. Topilsky, M., Siltzbach, L. E., Williams, M., and Glade, P. R.: *Lymphocyte response in sarcoidosis*. The Lancet. pp 117–120, Jan 15, 1972.

99. Douglas, S. D., Schmidt, M. E., and Siltzbach, L. E.: *Monocyte receptor activity in normal individuals and patients with sarcoidosis*. Immunological Communications. 1(1):25–38, 1972.

100. Teirstein, A. S., Siltzbach, L. E.: *Sarcoidosis of the upper lung fields simulating pulmonary tuberculosis*. CHEST 64:303–308, Sept. 1973.

101. Siltzbach, L. E.: *Bilateral Hilar Lymphadenopathy*. (Letter) The Lancet. pp 879–880, April 21, 1973.

102. Siltzbach, L. E.: *Kveim-Siltzbach Test Vindicated*. (Letter). The Lancet. p 188 Jan 22, 1972.

103. Stein E., Jackler, I., Stimmel, B., Stein, W., and Siltzbach, L. E.: *Asymptomatic electrocardiographic alterations in sarcoidosis*. Amer. Heart Journal. Vol 86, #4, pp 474–477, October 1973.

104. Miller, A., Teirstein, A. S., Jackler, I., Chuang, M., and Siltzbach, L. E.: *Airway function in chronic pulmonary sarcoidosis with fibrosis*. Am. Rev. Resp. Dis. 109:179–189, 1974.

105. Taub, R. N., Siltzbach, L. E.: *Induction of granulomas in mice by injection of human sarcoid and ileitis homogenates*. Proceedings of the VIth International Conference on Sarcoidosis. K. Iwai and Y. Hosoda (eds.) Univ of Tokyo Press. pp. 20–21, 1974.

106. Douglas, S. D., and Siltzbach, L. E.: *Electron microscopy of Kveim biopsies in Sarcoidosis*. Proceedings of the VIth International Conference on Sarcoidosis. K. Iwai and Y. Hosoda (eds.) Univ. of Tokyo Press. pp. 54–56, 1974.

107. Siltzbach, L. E.: *Surveillance of Kveim test results*. Proceedings of the VI International Conference on Sarcoidosis. K. Iwai and Y. Hosoda (eds.) Univ. of Tokyo Press. pp. 79–83, 1974.

108. Siltzbach, L. E., and Sarkar, T. K. *Kveim reactivity and patterns of organ involvement in Sarcoidosis.* Proceedings of the VI International Conference on Sarcoidosis. K. Iwai and Y. Hosoda (eds.) Univ. of Tokyo Press. pp. 88–89, 1974.

109. Douglas, S. D., Schmidt, M. E. and Siltzbach, L. E.: *Peripheral blood monocyte IgG and C3 membrane receptor activity in patients with sarcoidosis.* Proceedings of the VI International Conference on Sarcoidosis. K. Iwai and Y. Hosoda (eds.) Univ. of Tokyo Press. pp. 186–188, 1974.

110. Stein, E., Jackler, I., Stimmel, B., Stein, W., and Siltzbach, L. E.: *Asymptomatic electrocardiographic alterations in eighty patients with sarcoidosis.* Proceedings of the VI International Conference on Sarcoidosis. K. Iwai and Y. Hosoda (eds.) Univ. of Tokyo Press. pp. 360–364, 1974.

111. Chusid, E. L., Vieira, L. O. B. D., Siltzbach, L. E.: *Sarcoidosis of the pleura.* Proceedings of the VI International Conference on Sarcoidosis. K. Iwai and Y. Hosoda (eds.) Univ. of Tokyo Press. pp. 373–378 1974.

112. Miller, A., Teirstein, A. S., Jackler, I., Siltzbach, L. E.: *Evidence of airway involvement in late pulmonary sarcoidosis using flow-volume curves and N_2 washout.* Proceedings of the VI International Conference on Sarcoidosis. K. Iwai and Y. Hosoda (eds.) Univ. of Tokyo Press. pp. 421–424, 1974.

113. Teirstein, A. S., and Siltzbach, L. E.: *Sarcoidosis with accurately dated onset—A study of 100 patients with initial erythema nodosum.* Proceedings of the VI International Conference on Sarcoidosis. K. Iwai and Y. Hosoda (eds.) Univ. of Tokyo Press. pp. 453–455, 1974.

114. Siltzbach, L. E.: *Reliability of the Kveim reaction in Sarcoidosis.* (Unpublished manuscript) Annual meeting, Massachusetts Thoracic Society. April 19, 1974.

115. Ramachandar, K., Douglas, S. D., Siltzbach, L. E. and Taub, R. N.: *Short Communications—Peripheral blood lymphocyte subpopulations in sarcoidosis.* Cellular Immunology 16:422–426, 1975.

116. Siltzbach, L. E.: *Reaction to Kveim-test material in sarcoidosis.* (Letter) The Lancet. p. 808, April 5, 1975.

117. Chusid, E. L., and Siltzbach, L. E.: *Sarcoidosis of the Pleura.* Ann. Int. Med. 81:190–194, 1974.

118. Siltzbach, L. E., James, D. G., Neville, E., Turiaf, J., Battesti, J. P., Sharma, O. P., Hosoda, Y., Mikami, R., Odaka, M.: *Course and prognosis of Sarcoidosis around the world.* The Amer. J. of Med. 57:847–852, Dec. 1974.

119. James, D. G. and Siltzbach, L. E.: *Sarcoidosis* (Chapter) Current Dermatologic Management. S. Maddin (ed.) The C. V. Mosby Company. 2nd ed. pp. 278–280, 1975.

120. Siltzbach, L. E.: *Kveim Test in Sarcoidosis* (Letter) New Eng. Jour. of Med. Vol. 293, #21, pp. 1103–1104, 1975.

121. Siltzbach, L. E.: *The Kveim test is a reliable means of diagnosing sarcoidosis.* Controversy in Internal Medicine II. W. B. Saunders Co. pp. 349–358, 1974.

122. Siltzbach, L. E.: Chapter—*Sarcoidosis in Pregnancy.* Gutmacher, Alan F., and Rovinsky, Joseph J.: Complications in Pregnancy. Waverly Press, Baltimore. 3rd ed. 1976 in press.

123. Siltzbach, L. E.: Introductory remarks: *The challenge of the granulomatous disorders in man.* Seventh International Conference on Sarcoidosis and other Granulomatous Disorders. L. E. Siltzbach (ed.) Annals of the New York Academy of Sciences. 278:1–2, 1976.

124. Douglas, S. D., Schmidt, M. E., Daughday, C. C. and Siltzbach, L. E.: *Kinetics of monocyte receptor activity for immunoproteins in patients with sarcoidosis.* Seventh International Conference on Sarcoidosis and other Granulomatous Disorders. L. E. Siltzbach (Ed.) Annals of the New York Academy of Sciences, 278:190–200, 1976.

125. Miller, A., Chuang, M. T., Teirstein, A. S. and Siltzbach, L. E.: *Pulmonary function in stage I and II pulmonary sarcoidosis.* Seventh International Conference on Sarcoidosis and other Granulomatous Disorders. L. E. Siltzbach (ed.) Annals of the New York Academy of Sciences, 278:292–300, 1976.

126. James, D. G., Neville, E., Siltzbach, L. E., Turiaf, J., Sharma, O. P., Hosoda, Y., Mikami, R., Odaka, M., Villar, T., Djuric, B., Douglas, A., Middleton, W., Karlish, A., Blasi, A., Olivieri, D., Press, P.: *Sarcoidosis around the world, A cooperative study.* Seventh International Conference on Sarcoidosis and other Granulomatous Disorders. L. E. Siltzbach (ed.) Annals of the New York Academy of Sciences, 278:321–334, 1976.

127. Teirstein, A. S., Berger, H. W. and Siltzbach, L. E.: *Sarcoidosis in three population groups in New York City.* Seventh International Conference on Sarcoidosis and other Granulomatous Disorders. L. E. Siltzbach (ed.) Annals of the New York Academy of Sciences, 278:371–376, 1976.

128. Stein, E., Stimmel, B., Siltzbach, L. E.: *Clinical course of cardiac sarcoidosis.* Seventh International

Conference on Sarcoidosis and other Granulomatous Disorders. L. E. Siltzbach (ed.) Annals of the New York Academy of Sciences, 278:470–474, 1976.

129. Teirstein, A. S., Miller, A., Chuang, M. T., Siltzbach, L. E.: *Flexible bronchoscopic biopsy of lung and bronchial wall in intrathoracic sarcoidosis*. Seventh International Conference on Sarcoidosis and other Granulomatous Disorders. L. E. Siltzbach (ed.) Annals of the New York Acad. Sci., 278: 522–527, 1976.

130. Taub, R. N., Sachar, B., Janowitz, H., Siltzbach, L. E.: *Induction of granulomas in mice by innoculation of tissue homogenates from patients with inflammatory bowel diseases and sarcoidosis*. Seventh International Conference on Sarcoidosis and other Granulomatous Disorders. L. E. Siltzbach (ed.) Annals of the New York Academy of Sciences, 278:560–564, 1976.

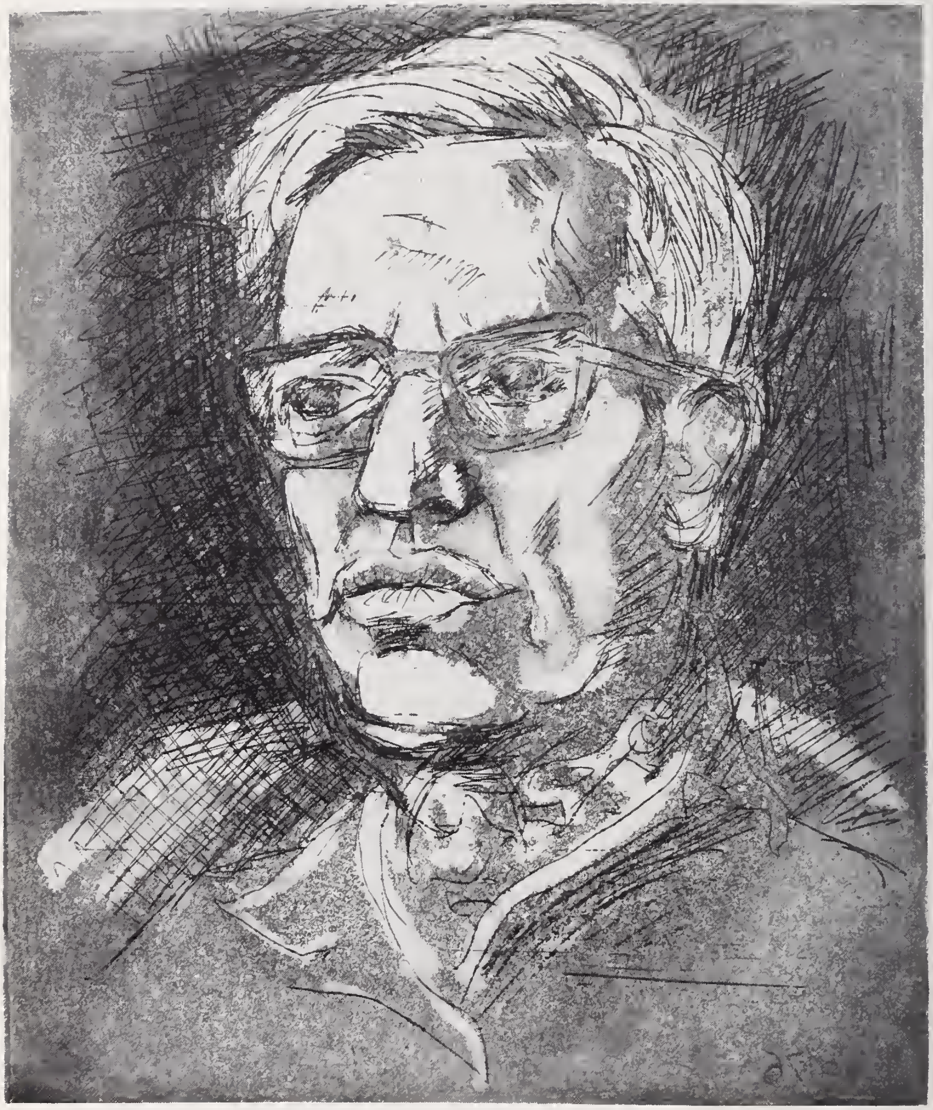
131. Siltzbach, L. E.: *Qualities and behavior of satisfactory Kveim suspensions*. Seventh International Conference on Sarcoidosis and other Granulomatous Disorders. L. E. Siltzbach (ed.) Annals of the New York Academy of Sciences, 278:665–669, 1976.

132. D. G. James, Turiaf, J., Hosoda, Y., Jones Williams, W., Israel, H. L., Douglas, A. C., and Siltzbach, L. E.: Description of sarcoidosis: *Report of the subcommittee on Classification and Definition*. Seventh International Conference on Sarcoidosis and other Granulomatous Disorders. L. E. Siltzbach (ed.) Annals of the New York Academy of Sciences, 278:742, 1976.

133. Siltzbach, L. E.: *Sarcoidosis*. Method of Louis E. Siltzbach, M.D. Chapter in Current Therapy. Conn (ed.) W. B. Saunders Co., 28th edition, pp. 144–146, 1976.

134. Siltzbach, L. E.: *Sarcoidosis* (chapter) Immunological Diseases. Samter (ed.) Little Brown and Co., 3rd edition, 1977, in press.

135. Siltzbach, Louis E.: *Sarcoidosis*. (Chapter) Pulmonary Diseases. A. P. Fishman (ed.) McGraw-Hill, New York. 1st edition, 1978, in press.



LOUIS E. SILTZBACH, M.D.

"Lou"

D. GERAINT JAMES

Louis Siltzbach was born on the 27th of May, 1906 in New York City. His upbringing and education derived from this international background and he has spent his lifetime repaying this rich heritage by working in the city and adding considerably to its professional and cultural standards. A combination of rare intellect, generosity of mind, and a warm love of the city enable the Siltzbachs of this world to keep New York City truly great.

In the year of his birth Clement von Pirquet introduced the term allergy into medicine, the first international conference for cancer research was held at Heidelberg and Frankfurt, Upton Sinclair portrayed life in the raw in Chicago in *The Jungle*, and Cezanne painted "Still life with Chairs, Bottles and Apples" and "Portrait of Vallier." This was the memorable year in which Picasso composed "Gertrude Stein," Ralph Vaughan Williams produced "Three Norfolk Rhapsodies," Rousseau painted "Summer, the Pasture," and the Fauves Movement was started by Matisse and Derain. Winston Churchill wrote the biography of his father "Lord Randolph Churchill," Conrad provided "Mirror of the Sea," Walter de la Mare his "Poems." Fowler published *The King's English*, and Galsworthy gave us *The Man of Property*.

In the world at large, 1906 was the year in which San Francisco suffered a severe earthquake followed by widespread fire, Norwegian explorer Roald Amundsen traversed the Northwest Passage, the 12-mile Simplon tunnel was opened, and the Lusitania and battleship HMS Dreadnought were launched. And Louis Siltzbach was also launched along the road to the City College, Columbia University, Long Island Medical College, Lebanon and Montefiore Hospitals, The Mount Sinai Hospital, and the Rockefeller Institute. Another road took him in 1932–33 to the University of Vienna. There he studied pulmonary pathology with Professor J. Erdheim. He studied in Europe during fateful years of world history for in 1932 he saw Dollfuss become Chancellor of Austria, De Valera came to power in Eire, President Doumer of France was assassinated, and Roosevelt became President of the USA. As Lou left Vienna in 1933, Hitler was appointed Chancellor of Germany, the Reichstag was on fire in Berlin, the Austrians prohibited tourist traffic from Germany as an anti-Nazi move, the Falange was founded in Spain, and Mosley was in charge of an equivalent British Union of Fascists. As the dark clouds accumulated over Europe so the sun shone on his return to New York for, by way of a welcome home, prohibition was repealed.

The rest of his story is well known through his academic achievements, scholarly writings, international lectureships, and profound influence on the world sarcoidosis movement. His earliest articles were on serial sedimentation rates in pulmonary tuberculosis, the rehabilitation of the tuberculous, the silicosis hazard, bronchiectasis, and pulmonary fibrosis; his latter day writings have influenced world thought on all aspects of sarcoidosis, culminating in his editorship of the authoritative 751-page monograph, *Transactions of the Seventh International Conference on Sarcoidosis and Other Granulomatous Disorders*, published by the New York Academy of Sciences as Annals of the New York Acadamy of Sciences, Volume 278 (1976).

More will come, for we still await his own personal experience in a monograph on sarcoidosis but, for the present, enough is a feast and this is certainly so with his Seventh International Congress on Sarcoidosis which was held, fittingly, in his birthplace, New York City. He has ploughed back into the city more than enough.

The Mount Sinai Journal of Medicine
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Louis by Hansi

HANSI BOHM

I have painted his portrait in oils and modeled it in clay, drawn and engraved it; but now, to describe the many-faceted features of his personality, I have to sketch them out in words.

For a man whose passion in life is his work, his interests are extraordinarily diversified and broad. His power of concentration is such that, once immersed in a book, all else is forgotten; he has applied it to a great many books, for he is familiar with all the great literature the world over. His enviable memory allows him to recall the characters at will: they emerge in his imagination like living people with their own joys and sorrows, problems and failings—but at the same time as literary metaphors as well. It is this deeper understanding which makes the world of great writing hang together and form an interpretive image of life. Louis' favorites are Joyce, Proust, Henry James, and Faulkner—a fertile mind appreciating the subtle complexities of another and savoring superb handling of language.

He loves the theater, particularly in London, where Chekhov is played so beautifully, and Stoppard's and Pinter's plays are of such relevance to his own view of contemporary life.

Louis is an avid newspaper and magazine reader: on politics, science, archeology, literary criticism and—may I admit it—a keen television watcher of sport, particularly American football and tennis. He has great interest in journalism, and many good friends among journalists—the late Joe Liebling of the New Yorker and John Lardner of Newsweek were quite his favorites.

He derives profound pleasure from works of art, especially painting. I believe his great favorites are Rembrandt's "Prodigal Son" in the Hermitage in Leningrad; Goya's graphic work in the Prado; and Matisse and Picasso. He asserts that he was introduced to and appreciated the work of these modern masters before he knew anything about the Old Masters. This is a delightful piece of American radicalism, especially to European minds who work their way gradually from Michelangelo to an understanding of the avant garde. His appreciation is deepened by his own artistic pursuits for he has himself composed several oil paintings, water colors, and has also made a spirited sally into abstract expressionism.

Music plays a big part among his pleasures and relaxations. Playing the piano himself, he is a regular and enthusiastic concert-goer with a wide and informed knowledge of the musical literature. He most enjoys the Beethoven quartets, Mozart operas, Bach, the Rosenkavalier, Baroque and Renaissance music generally. And, of the avant garde, Stravinsky and Berg (Wozzek), Charles Ives, and Elliot Carter. I recall with pleasure his travels following the pilgrimage road from Canterbury (where he photographed all the glass) to Santiago di Compostelo. There is hardly a Romanesque cathedral or church in France or Spain left unvisited, unphotographed; his interest lies not only in the architecture but he is fascinated by the iconography and expressiveness of medieval sculpture and frescoes and he has made beautiful sets of slides of the tympani, choirstalls, and carved capitals. I have used quite a few of his sets in lectures on the history of art. His travels in the cause of archeology have taken him to Cambodia (the temples of Angkor Wat and Angkor Thom), to the caves of Lascaux, to Sicily, and to many other places.

One might think that beside all these interests and pursuits, little room would be left for the central theme of a physician's life. This is not so. Nothing, not the most alluring experience, can take precedence over the deep and sympathetic with his patients. And, coupled with the humane aspect of medicine goes the lifelong scientific curiosity about the roots of illness and their governing principles.

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Printed in U.S.A.

Mon Ami Louis Siltzbach

J. TURIAF

Louis Siltzbach est un ami que l'on aime rencontrer. Il est assurément un grand médecin et un chercheur de renommée mondiale. Mais la chaleur humaine qui émane de lui et sa vaste culture dans le domaine des arts rendent sa compagnie particulièrement enrichissante et agréable.

Je ne peux dire s'il est amateur de Pop music, mais je sais d'expérience qu'il est très attiré par les grandes oeuvres classiques, qu'il comprend et ressent merveilleusement. Les joies et les émotions que lui procurent la grande musique transcendent aimablement son âme. J'en eus la preuve quand, par un radieux après-midi de printemps, il m'entraina dans une une lointaine banlieue parisienne où un orchestre de musique de chambre avait au programme Bach, Mozart et Schubert.

Siltzbach est aussi un fervent de la peinture. Il en apprécie en amateur averti tous les aspects. Et je ne crois pas me tromper en supposant que le tendre attachement et l'admiration dont il entoure Madame Siltzbach tiennent pour une part au réel talent de peintre de sa charmante épouse. J'ai grâce à lui visité les riches musées de Washington et de New York. Ensemble, nous avons contemplé et commenté dans le ravissement les oeuvres des peintres les plus célèbres, des Primitifs aux champions de l'Art Abstrait. Il me souvient qu'un soir au vernissage d'une exposition de Primitifs italiens au Metropolitan Muséum de New-York, nous fumes tellement éblouis par les chefs d'oeuvre qui s'offraient à nos yeux que nous n'entendimes pas la sonnerie annonçant la fermeture des salles d'exposition. Nous en fumes chassés les derniers courtoisement mais fermement par de vigoureux cerbères. Mais en raison de l'heure tardive et dans la précipitation du départ, je n'eus pu récupérer mon pardessus aux vestiaires déjà fermés. J'étais, malgré ce contre-temps, très heureux de ma soirée. Le lendemain, je rentrai en possession, non sans mal, de mon manteau.

Louis Siltzbach a la passion des monuments anciens. A deux reprises au cours des dernières années, il a parcouru la France, selon un itinéraire préétabli, lui assurant la visite des cathédrales et des églises romanes qui en sont de prestigieux ornements. Il est revenu enchanté de ces randonnées. Siltzbach frémit d'aise et d'émotion chaque fois qu'il se trouve en présence d'un beau monument ancien quel qu'en soient l'aspect et le style. J'en eus la preuve en visitant avec lui par une chaude matinée d'été le chateau de Rambouillet, puis la cathédrale de Chartres. Nous étions attendus pour le déjeuner par des amis qui possèdent une ravissante gentilhommière dans la campagne beauceronne en lisière de la forêt de Rambouillet. Entièrement occupé à admirer l'architecture du célèbre chateau qu'il voyait pour la première fois et à en fixer les admirables reliefs sur des photographies qu'il prenait sans compter, Siltzbach, d'habitude si ponctel, oublia notre rendezvous. Nous arrivames fort en retard et assez penauds chez mes amis. Mais l'accueil chaleureux de nos hôtes et une délicieuse et euphorisante coupe de champagne bien frais nous rendirent gaité et entrain. Aussi fimes-nous honneur avec appétit au déjeuner, digne des meilleures tables françaises, qui nous fut offert.

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Printed in U.S.A.

Dr. Louis E. Siltzbach

ALFRED P. FISHMAN

I first met Dr. Siltzbach while I was a resident in medicine at The Mount Sinai Hospital and he was a young associate of Kelley Rabin. No one could shine when Rabin was in full glow. Therefore, Siltzbach was then a promising young man who had yet to demonstrate his own talents.

Quietly and effectively over the years he pursued clinical and investigative activities and I soon came to realize that I had been in the vicinity of one of the great chest men of our times. I would encounter clinical papers which summarized a large continuing clinical experience in chest medicine. But more importantly, I began to sense that of all the people working on sarcoidosis, Siltzbach was probably the one working most systematically and methodically toward an answer.

The answer to sarcoidosis is not yet with us. However, even though it may not arrive for a while, his own contributions to the subject, as well as the establishment of the famous Sarcoidosis Laboratory, will do a great deal to make further insights possible. At present the immunologic group at the University of Pennsylvania is deeply involved in exploring certain aspects of defense mechanisms in this disorder. Without Siltzbach and the Sarcoidosis Laboratory we would lack standards of reference which his laboratory provides. He continues to be generous in making these materials available and the fact that we receive these samples of homogenates and serum from him impresses us with the seriousness of the activity in which we are engaged.

It seems difficult to believe that Siltzbach is now at an age when one is thinking seriously of a commemorative volume for him. However, if there is to be one, I am happy to be allotted the privilege of expressing in it my admiration for him, for his work, and for the disciplined approach to medicine that he represents.

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Reminiscences of Dr. Louis E. Siltzbach

YUTAKA HOSODA

A fact will not be remembered as a fact unless it is described as it was. I feel it a duty to leave a note about what happened in the two recent international conferences on sarcoidosis.

A great loss in Tokyo

Late in August 1972, about two weeks before the opening of the VIth International Conference on Sarcoidosis to be held in Tokyo, I was shocked by a letter from Louis, dated August 16th, saying "It is with very deep regret indeed that I have to let you know so soon before our Tokyo Conference that my illness will prevent me from joining you all . . . ." This was not only his regret but a great loss for all of us. It was he who actually played a leading role in bringing the conference to Tokyo. Following the previous conference held in Prague in June 1969, he flew from Prague directly to Tokyo, accompanied by a well-known painter, Mrs. Siltzbach, to make an on-the-spot investigation of the conference facilities and to talk with our organizing team. The most impressive to him at that time were, as he told me later, the shouts of students demonstrating in the Kyoto University campus where we had an organizing meeting with him and where he gave a lecture on sarcoidosis. His lecture was not possible in universities in Tokyo because the student movements were at their height. Throughout the preparation period, I exchanged letters with him almost once a month. Finally, the Tokyo Conference was successfully completed with the cooperation of the International Committee members headed by Gerry James, as well as that of worldwide participants. Although his name does not appear in the official record in Tokyo, he should be remembered forever for his earnest devotion to the conference behind the scenes.

Two garden parties

On Sunday afternoon, October 5th 1975, one day before the opening of the VIIth International Conference on Sarcoidosis, a marvelous garden party was given by Dr. and Mrs. Siltzbach for the representatives of various countries in the garden of his lovely villa located in the outskirts of New York. His villa standing on the slope of a hill was surrounded by many old trees with beautiful yellow and red leaves, and the ground on which we walked was covered with fallen leaves. Eminent sarcoidologists gathered there to enjoy the company of a radiant host and hostess. Gerry James and Jacques Turiaf expressed their thanks on behalf of an international group of guests. This brilliant garden party reminded me of a similar one held in England on the occasion of the IIIrd International Congress of Dermatology, London 1896. A garden party was given by Dr. Jonathan Hutchinson and his daughter (his wife had died 10 years earlier) at his villa in Haslemere, which is located 43 miles south west from Waterloo Station. I tried to locate his old home in Haslemere. Although no longer owned by the family, I was delighted to find an elegant brick building where he lived in retirement, with the lawn just as it was for his garden party. In front, there was a small swimming pool in which he was reported to swim nearly until the end of his life. He was aged 68 years as president of the congress; his vice-presidents were Dr. C. Boeck, 51-years-old, and Dr. E. Besnier, 65-years-old.

The three famous sarcoidologists, together for the 1896 garden party in Haslemere, must have enjoyed it as much as we did the other given 80 years later by Dr. and Mrs. Siltzbach in their South Mountain Road country home.

References

1. Hunter, F. T.: Hutchinson-Boeck's Disease (Generalised "Sarcoidosis") Historical note and report of a case with apparent cure, N Engl J Med 214:346, 1936.
2. James, D. G.: Two Contrasting Nineteenth-Century Surgeon Dermatologists, Medical History XIV: 75, 1970.

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Louis Siltzbach

ANDREW DOUGLAS

It is said that a psychiatrist is a man who goes to the Folies-Bergere and looks at the audience. This is perhaps somewhat irrelevant to my personal reminiscences of Louis Siltzbach but not wholly so. I knew him through his writings before I met him and what I knew I admired. Later I was to appreciate the basis of this admiration, hence the tangential reference to our dedicated psychiatrist. In Louis Siltzbach one came to see the fusion of many functions and qualities—scientist, innovator, leader, teacher, zealot for truth, biologist, author, catalyst, and herald of things to come. Bestriding the sarcoid world like a Colossus (he himself would insist on a small "c" if he allowed the term), Louis Siltzbach has been the most identifiable name with sarcoidosis in our generation and it is characteristic of him that in his most recent publication he talks of new concepts in established things and frontiers yet to be crossed. Singlemindedness has been the main fiber of all great medical contributors. Our psychiatrist at the Folies had it in no greater measure than the man we salute today.

"The very first step toward success in any occupation is to become interested in it," *Sir William Osler*.

"Natural Religion has not foregone emotion. It elevates that spirit to the position of protagonist of a virility and dignity which otherwise the human figure could not possess. It raises the lowliest human being conjointly with the highest, Prometheus-like, to a rank of obligation and pathos which neither Moses in his lawgiving nor Job in all his sufferings could present. We have, because human, an inalienable prerogative of responsibility which we cannot devolve, no, not as once was thought, even upon the stars. We can share it only with each other," *Man on His Nature,* by Sir Charles Sherrington; *The Gifford Lectures*, Edinburgh 1937–8.

"And then the studious, the good and true, never suffer their minds to be warped by the passions of hatred and envy . . .; neither do they think it unworthy of them to change their opinion if truth and undoubted demonstration require them so to do; nor do they esteem it is discreditable to desert error, though sanctioned by the highest antiquity; for they know full well that to err, to be deceived, is human; that many things are discovered by accident, and that many may be learned indifferently from many quarters by an old man to a youth, by a person of understanding from one of inferior capacity. . . . I avow myself the partisan of truth alone; and I can indeed say that I have used all my endeavours, bestowed all my pains on an attempt to produce something that should be agreeable to the good, profitable to the learned, and useful to letters," *William Harvey*, London 1628.

We can see Louis Siltzbach in all of these.

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A Distant Relation

J. D. STOECKLE

I met Dr. Siltzbach just once. As so often happens between colleagues in different cities, the encounter was at a medical meeting, a small informal one, not in his New York or our Boston but in Philadelphia. We met with Drs. H. Hardy, G. James, H. Israel and M. Sones—about the Kviem test.

I was most impressed by Dr. Siltzbach's personal friendliness and, in discussion, with his wide general knowledge. Such isolated face-to-face encounters are hardly sufficient for knowing a person, certainly not Dr. Siltzbach. But our distant relation was made of other stuff. Most of it was one-sided as relations so often are, my reading of his papers, but some was also two-way, our correspondence over a project to test the Kviem antigen in beryllium patients. Out of these remote connections were two very good things, one a study, the other my improved medical practice.

In the first instance, patients with beryllium disease under the care of Dr. Hardy and myself were tested with the Kviem antigen from Dr. Siltzbach's laboratory at Mount Sinai and the Rockefeller Institute; Dr. David Freiman examined the biopsies. Everything went smoothly because the materials came promptly, the protocol was simple, and the patients cooperated; we were able to complete the testing over several months. Beryllium patients did not react (1).

More important has been the second outcome, my use of one of Dr. Siltzbach's papers to help explain sarcoidosis to patients (2). How does one explain sarcoidosis, or for that matter, any disease whose etiology is uncertain, to patients whose concepts of disease hardly approach the sophistication of "scientific" medical ideas about "inflammation," "granuloma," and "fibrosis"? I am not sure I yet know how to frame the answers, but Dr. Siltzbach's paper has helped. A crisp overview of sarcoidosis for a professional audience, the article was also useful to me in the task of communicating with patients, in explaining their diagnosis, treatment, and prognosis. The clear pictorial schema of the course and anatomical location of the disease was information that patients could "see," a visual description which has always seemed better than words alone.

Now I am not sure that Dr. Siltzbach intended his paper for this doctor-patient use. I surmise he meant it to be the pedagogic paper it was, containing old and new knowledge organized for the doctor in the task of medical diagnosis and background information for the doctor's perspective as he treats the patient. I doubt he thought the paper's influence might spill over, that one reader-practitioner might use it regularly for what is patient education, the explaining of illness, or that his work might not only get into the doctor's but also the patient's mind where "what you understand is what you have and how you feel." Because of Dr. Siltzbach, I think my patients have understood more and are "better." Now that he is an emeritus professor he might like to know these effects of a distant relation.

References

1. Siltzbach, L.: The Kviem Test in Tuberculosis, Beryllium Disease, Leprosy and Sarcoidosis, Am Rev Resp Dis 90:308, 1964.
2. Siltzbach, L. Current Thoughts on the Epidemiology and Etiology of Sarcoidosis, Am J Med 39:361, 1965.

The Mount Sinai Journal of Medicine
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Printed in U.S.A.

Croeso

W. JONES WILLIAMS

"Croeso cynnes i chwi gyd i Gymru." This is the Welsh for a warm welcome to all readers of this Festschrift, many of whom we hope will visit Cardiff from the 11th to 15th September 1978 to participate in the 8th International Conference on Sarcoidosis (Fig. 1). Typical of Louis' international outlook, he has already visited Cardiff to inspect us. Now that we carry his stamp of approval on our shoulder, we feel free to extend our welcome to all the readers of his festschrift. We intend to have a five-day, ten-session scientific meeting on sarcoidosis and other granulomatous disorders. Cardiff is an elegant university city with a large selection of accommodations. Write to me for details and let me know whether you plan to submit a communication.

INTERNATIONAL CONFERENCE ON SARCOIDOSIS
8th
ICS
CARDIFF 1978

William Jones Williams, M.D.
International Conference on Sarcoidosis
University Hospital of Wales
Cardiff CF4 4XX
Wales, U.K.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November–December, 1977
Printed in U.S.A.

Louis E. Siltzbach, M.D.: Pulmonary Division

ALVIN S. TEIRSTEIN, M.D.

Since 1953, I have had the opportunity to observe Lou Siltzbach stripped of professional trappings, sleeves rolled-up, bent over a manuscript and microscope, and in intense thoughtful discussion. In the early years, I wondered why this serious, rather austere man prowled the hospital corridors injecting a muddy brown fluid into the forearms of my patients. With time, I recognized a unique scholar and scientist who by his example taught me the importance of careful, precise, personal investigation. With remarkable tenacity and devotion he relentlessly compiled a body of data that led him to landmark expositions concerning the nature of sarcoidosis. In great measure, we are indebted to Lou Siltzbach for our understanding of the clinical presentation, diagnosis and treatment of this disease. In 1954 (1) he irrefutably established the specific diagnostic role of the Kveim test. Later, when his work was challenged, he was able decisively to prove the validity of his studies. This valuable diagnostic procedure has quite correctly acquired the title, Kveim-Siltzbach test. His description in 1955 of the three radiographic stages of sarcoidosis brought a chronological order to seemingly unrelated clinical syndromes (2). Indeed, one of his monumental accomplishments has been a clear integration of the Kveim-Siltzbach test, chest radiographic abnormalities, and extrathoracic manifestations into a rational time table of sarcoidosis. Simultaneously, he was among the first to demonstrate the efficacy of adrenal corticosteroids in suppressing granuloma formation and establishing a rational schema for therapy (3). Ever the scholar, he has augmented his classic knowledge of pathology and clinical medicine with a mastery of modern immunology and physiology, collaborating in important studies of lymphocyte and monocyte function in sarcoidosis, the experimental production of granulomas in animal models and the physiologic staging of sarcoidosis. Thus, Lou Siltzbach is established in the line of Boeck, Schaumann, and Kveim as a preeminent investigator of sarcoidosis.

Shunning the material benefits of a large all-consuming private practice, Lou Siltzbach single-mindedly prepared for his life's work by continuing his studies with postgraduate research fellowships in pathology at the University of Vienna and in tuberculosis at Montefiore Hospital. With recognition of his work came professorships at Columbia University College of Physicians and Surgeons and Mount Sinai School of Medicine, and a long association with the Rockefeller Institute as Consulting Physician.

While his mark is indelibly established by his published works and his words spoken at universities and congresses around the world, his greatest achievement is measured in the large number of students who have come to study with him from every continent. In the words of Chaucer, ". . . and gladly wolde he learne, and gladly teche" (*The Canterbury Tales,* "Prologue," 1.308).

Bibliography

1. Siltzbach, L. E., Ehrlich, J. C.: The Nickerson-Kveim reaction in sarcoidosis. Am. J. Med. 16:791–803, 1954.
2. Siltzbach, L. E.: Pulmonary Sarcoidosis. Am. J. Surg. 89:556–568, 1958.
3. Siltzbach, L. E.: Effects of cortisone in sarcoidosis; a study of 13 patients. Am. J. Med., 12:139, 1952.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

The Sarcoidosis Movement

D. GERAINT JAMES

The Sarcoidosis Movement

The historical background of sarcoidosis has been told and retold in a series of papers in the Transactions of the Fifth International Conference held in Prague (1969). They bring to life the contributions of Robert Willan, Jonathan Hutchinson, the Boecks, Besnier and Pautrier, Tenneson, Schaumann, Kreibich, and Kveim. Louis Siltzbach's contributions also provide a milestone in the evolution of knowledge concerning sarcoidosis. Apart from his own scientific and academic advances, he has also kept intact and viable an entire sarcoidosis movement by his painstaking efforts as secretary of the International Committee on Sarcoidosis. This is an unpaid thankless office which Louis has succeeded in converting into a highly effective instrument for coordinating conferences and disseminating news and knowledge on sarcoidosis around the world. It has led to seven World Conferences on sarcoidosis with an eighth on the way (Table I).

First Conference (1958)

The Olympic torch was lit and the first conference was held from 30 June to 2 July 1958 in London. Until that time we had read each other's articles but we did not know each other. We met in a spirit of cordiality and camaraderie, and this spirit has pervaded all subsequent conferences (Fig. 1).

Second Conference (1960)

This was arranged by the United States National Academy of Sciences–United States National Research Council in Washington D.C. from 1 to 3 June 1960, and masterminded by Dr. Martin Cummings. It was a model for all conferences—intimate (we were just 45 active participants), academic, comfortable, genial, and fruitful (out of it came a working definition and exemplary proceedings).

Martin Cummings did more than just organize a conference and keep the Olympic torch burning. His enthusiastic support also led to the publication of the unique bibliography on sarcoidosis, spanning 1878–1963 initially, and thereafter brought up to date by the United States National Library of Medicine. He is a splendid Director and a good friend of sarcoidosis research.

Third Conference (1963)

Sven Lofgren was the outstanding organizer of the Stockholm meeting held from 11 to 14 September 1963 under the auspices of the International Union against tuberculosis. The representatives of 26 countries are listed in the

From the Royal Northern Hospital, London, England, N76LD.

TABLE I

International Conferences on Sarcoidosis

Year	City	Organizer	Number of Delegates	Number of Countries Represented	Number of Communications	Proceedings
1958	London	D. Geraint James	22	8	22	Taped but not Published
1960	Washington	Martin Cummings	45	10	30	Amer. Rev. resp. Dis. (1961) 84: Suppl. 5
1963	Stockholm	Sven Lofgren	150	26	98	Acta med. Scand. (1964) Suppl. 425: pp. 309
1966	Paris	J. Turiaf	275	33	109	Rapports (1967) Masson & Cie, Paris, pp. 782
1969	Prague	Ladislav Levinsky	300	37	127	Published 1971. pp. 655 Universita Karlova Praha
1972	Tokyo	Yutaka Hosoda	300	22	115	Published 1974. pp. 666 University of Tokyo Press
1975	New York	Louis Siltzbach			80	Annals N.Y. Acad. Sci. (1976) 278: 1-751
1978	Cardiff	W. Jones Williams				

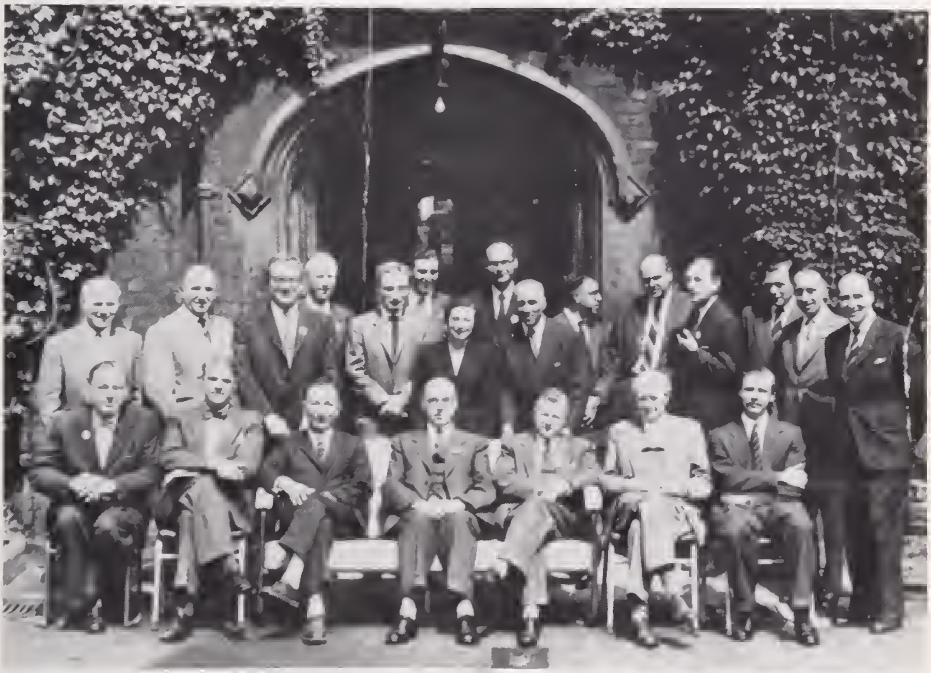

FIG. 1. There were only 22 participants in the 1958 London Conference, with one woman, Dr. Ingrid Gilg.

excellent proceedings, edited by Sven Lofgren with the able assistance of Hans Bauer and Barbro Weist (Fig. 2).

Fourth Conference (1966)

The Paris Conference was held from 12 to 15 September 1966 under the genial presidency of Professor J. Turiaf (Fig. 3). The participants had swelled in number to 275. The daytime conferences were of a high interna-

FIG. 2. Large international participation in the Stockholm Conference (1963).

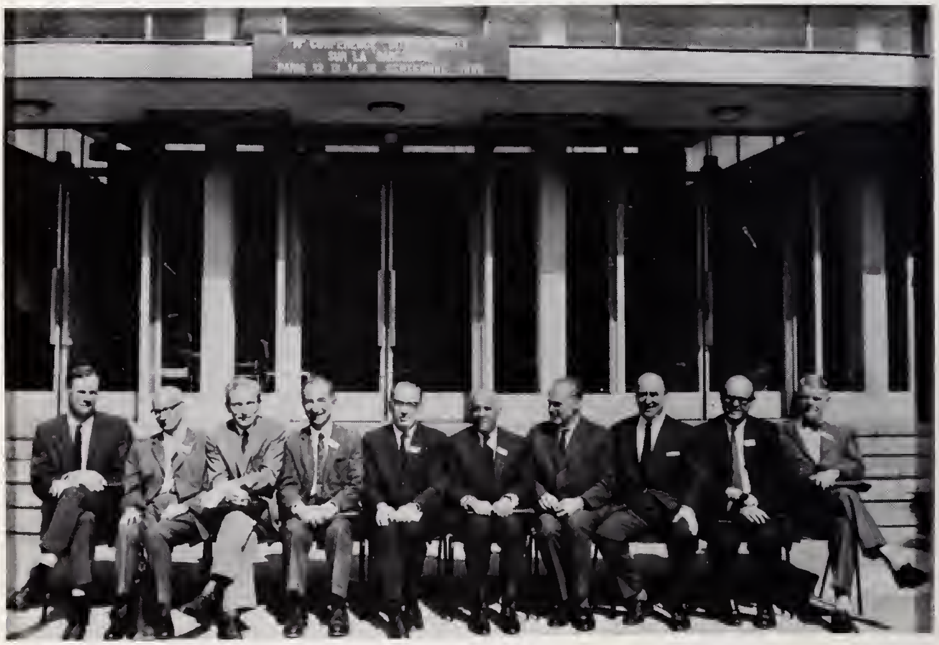

FIG. 3. The International Committee on Sarcoidosis, assembled for the Paris Conference in 1966. From left to right: T. H. Hurley (Melbourne), E. A. Uehlinger (Zurich), J. S. Chapman (Dallas), H. Israel (Philadelphia), L. E. Siltzbach (New York), J.Turiaf (Paris), L. Levinsky (Prague), D. Geraint James (London), M. M. Cummings (Washington D.C.), and S. Lofgren (Stockholm).

tional academic standard and the evenings were, as might be expected, a gay social whirl. The proceedings are a voluminous, information-crammed 782 pages, opening with Louis Siltzbach's inaugural address in perfect French and ending with Sven Lofgren's chairmanship of the last session which was very much a "free for all" on treatments in vogue at that time. Interestingly enough, these treatments and their indications still remain unchanged now, ten years later.

Fifth Conference (1969)

The Prague Conference was held from 16 to 21 June 1969 under the presidency of Professor Ladislav Levinsky. Three hundred delegates from 37 countries were in attendance. It was also the XIVth Scientific Conference of the Medical Faculty of Charles University, so the inaugural ceremony took place in the venerable Carolinum, beflagged with emblems of the state and of this lovely old University (Fig. 4). It was in this Aula Magna, the assembly hall of Charles university since the 14th century, that Purkyne (1787–1869) made the historic first pronouncement that animal cells contained a nucleus. In the year 1969, we were commemorating the hundredth anniversary of the death of this Czech founder of modern physiology, histology, and microscopy. His motto was "Knowledge is Power," and this is surely a good way of describing Levinsky's 653-page Transactions of this conference.

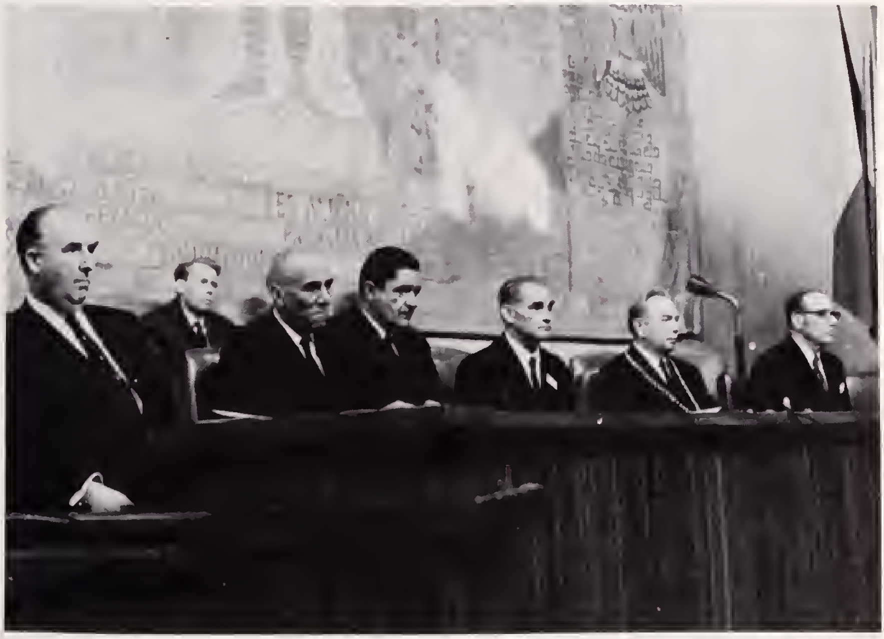

FIG. 4. The inaugural ceremony at the Prague Conference (1969) in the venerable Aula Magna, the 14th century assembly hall of Charles University.

Sixth Conference (1972)

The Tokyo Conference was large, flamboyant, and the only one to produce a special postal stamp. It is dated 47.9.15 for 15 September 1972, and alongside is flourished "VI ICS." This congress was superbly well organized by Yutaka Hosoda and held in Tokyo with a postcongress meeting on treatment in Kyoto.

This is the only conference Louis Siltzbach missed. Ill health kept him in New York; he was widely quoted and sorely missed.

Seventh Conference (1975)

The conference held from 6 to 10 October 1975 in New York City under the presidency of Louis Siltzbach was the largest and most sophisticated, introducing as it did the most advanced immunological techniques not only for sarcoidosis but also for other granulomatous disorders. Not only was Louis the Conference Chairman but also the editor of the Transactions, so in his usual effective way a 751 page monograph of this congress was published as Volume 278 (1976) of the Annals of the New York Academy of Sciences within one year of the conference. It contains 83 articles on all aspects—immunology, animal models and virology, physiology, epidemiology, diagnostic tests, treatment, and other granulomatous disorders. A worthy monument of an outstanding conference.

Eight conference (1978)

Please make a note in your diaries that the next conference is to be held from 11 to 15 September 1978 in Cardiff, the beautiful capital of Wales. Dr. W. Jones Williams, the organizing driving force, is a pathologist who has made substantial contributions to our knowledge of the ultrastructure, biochemistry and immunology of sarcoidosis, beryllium disease, and Crohn's disease.

He will give you a fresh Celtic insight to sarcoidosis and other granulomatous disorders.

The Mount Sinai Journal of Medicine
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Scholarship and Sarcoidosis

MARTIN M. CUMMINGS, M.D.

No syndrome or disease entity has been more thoroughly described in medical literature than sarcoidosis. Yet we are still unable to establish clearly its etiology. More than 5,000 clinical and scientific papers have been published since 1878, at which time Jonathan Hutchinson first described patients suffering from what he later called "Mortimer's malady" (lupus vulgaris multiplex nonulcerans and nonserpigeneous).

The riddle of sarcoidosis has fascinated many scholarly clinicians and scientists, as the remarkable "Bibliography on Sarcoidosis" published by Mandel, Thomas, Carman, and McGovern in 1964 makes clear. Dr. Louis E. Siltzbach, whom we honor in this Festschrift, contributed extensively to this literature. Since his first article appeared in 1951, Dr. Siltzbach has published more than 100 descriptive and informative papers on sarcoidosis, which demonstrate a depth of scholarship frequently lacking in scientific and clinical writing today. His extensive references are expressions of his comprehensive knowledge of all aspects of the disease he has studied so carefully for 25 years.

But why should anyone be concerned with such matters as bibliography when so much remains to be learned about sarcoidosis itself? Fielding H. Garrison, America's first professional medical historian, wrote that bibliographic work "puts out eyes and bores holes in the brain," but, he continued, "those of us with preoccupations and obsessions pay little attention to minor inconveniences." Sarcoidosis scholars know that they must be aware of the accumulated scientific findings of the past in order to devise new approaches to future studies. Retrospective studies of the literature also provide humanistic insights into the men who have been fascinated by complex clinical problems such as those presented in sarcoidosis.

Because of its various clinical manifestations, no disease has more eponyms associated with it than does sarcoidosis. We can mention a few: "Mortimer's malady," named after Hutchinson's patient, "Boeck's sarcoid," "Schaumann's syndrome," "Jungling's syndrome," "Besnier-Boeck-Schaumann syndrome," "Lofgren's syndrome," "Besnier-Tenneson syndrome." Although eponymic syndromes are not generally applauded in medicine, they do reflect some recognition of the persons who have contributed a new observation or description that enriches the overall picture of a complex clinical entity.

Even the skin test employed for the diagnosis of sarcoidosis has its eponymic history. Originally conceiving it to be a virus disease, Williams and Nickerson in 1935 used a sterilized, heated saline suspension of sarcoid skin tissue to obtain a papular reaction. This was later refined by Kveim in 1941 when he demonstrated that a heat-killed suspension of sarcoid lymph node produced delayed histologic evidence of sarcoid reaction at the site of

From the Public Health Service, National Institutes of Health, Bethesda, Maryland 20014.

injection. For twenty years this was known as the Nickerson-Kveim test. Now it is known as the Kveim-Siltzbach reaction, following Siltzbach's painstaking studies of the diagnostic value of the test that utilizes a standardized antigen prepared from a spleen taken from a patient with sarcoidosis.

The history of sarcoidosis shows an equal balance of successes and failures. The successes are principally in the field of clinical description and to a lesser extent in therapy; the failures lie in the succession of theories and research efforts attempting to elucidate etiology.

In reviewing sarcoidosis and scholarship, there is good reason to mention the series of international conferences first stimulated by Dr. D. Geraint James in London in 1958. Starting with a small group of keenly interested physicians who gave informal reports of their studies and experiences, these triennial meetings have culminated in a series of formal transactions which meet the highest standards of scientific publication. One cannot avoid being impressed with the historical perspective provided by these reports. They have also drawn into the interested community of scholars persons with new talents and scientific backgrounds who will undoubtedly contribute to the ultimate solution of the problem of the etiology of the disease.

I can only hope that the solution will be found during my lifetime because no problem has intrigued and confused me more. I suspect that this wish is shared by Dr. Siltzbach, as well as the colleagues and devotees who have burned the midnight oil puzzling over and dreaming of means to bring forth a solution.

References

1. Hutchinson, J.: Cases of Mortimer's Malady (Lupus Vulgaris Multiplex Non-Ulcerans and Non-Serpigeneous), Arch Surg (London) 9:307–14, 1898.
2. Mandel, Wm., Thomas, J. H., Carman, C. I., and McGovern, J. P.: *Bibliography on Sarcoidosis; 1878–1963*, U. S. Dept. of Health, Education, and Welfare, Public Health Service Publication No. 1213, Washington, D. C. 1964.
3. Boeck, C.: Multipelt Benignt Hudsarkoid ("Multiple benign skin sarcoid"), Nor Mag Laegevid 14:1321–34, 1899.
4. Tenneson, M.: Lupus Pernio, Ann Dermatol Syphiligr (Paris) Ser 3,3:1142–4, 1892.
5. Schaumann, J.: Etude sur le lupus pernio et ses rapports avec les sarcoides et la tuberculose (Study of Lupus pernio and Its Relationship to Sarcoidosis and Tuberculosis), Ann Dermatol Syphiligr (Paris) 6:357–73, 1916–1917.
6. Jungling, O.: Osteitis tuberculosa multiplex cystica (eine eigenartige form der knochentuberkulose) (Osteitis tuberculosa multiplex cystica: A Peculiar Form of Bone Tuberculosis), Fortschr Roentgenstr 27:375–83, 1919–1921.
7. Lofgren, S.: Morbus Besnier-Boeck-Schaumann (Sarcoidosis): klinik (Besnier-Boeck-Schaumann Disease—Sarcoidosis: Clinical Aspects), Nord Med 52:976–81, 1954.
8. James, D. G.: Clinical Concepts of Sarcoidosis, Amer Rev Resp Dis 84 (5 pt 2): 14–19, 1961.
9. Williams, R. H. and Nickerson, D. A.: Skin reactions in Sarcoid, Proc Soc Exp Biol Med 33:403–5, 1935.
10. Kveim, A.: En ny og specifikk kutan-reaksjon ved Boecks sarcoid, en forelobig meddelelse (On a New and Specific Cutaneous Reaction in Boeck's Sarcoid; A Preliminary Report), Nord Med 9:169–72, 1941.
11. Siltzbach, L. E.: The Kveim Test: Historical Aspects, In *Proc. Vth Conf. on Sarcoidosis*. Edited by L. Lewinsky and F. Macholda. Univ. Karlova, Prague 1971, pp. 66–67.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Kveim and Siltzbach

ANDREW C. DOUGLAS.

"A puzzle wrapped in an enigma" is the way in which Winston Churchill described the behavior of one of the wartime allies; it could be applied equally to the multisystem granulomatous disorder of sarcoidosis and the skin test used in its specific diagnosis. Though numerous investigators have made outstanding contributions to knowledge of the response in the sarcoid subject to intradermal injection of an appropriate sarcoid tissue suspension, none has equaled or surpassed those of Kveim and Siltzbach and it is fitting, even in these days when eponyms tend to find little favor, that their names are linked in designation of the test. The completeness of Kveim's description of the test in 1941 (1) and its subsequently proven accuracy by Danbolt, Putkonen and Nelson (2) among others justly gives him pride of place in its discovery. However, mention should also be made of the earlier work of Williams and Nickerson in 1935, regrettably inconclusive because of the failure to follow through initial observations (and incomplete since Nickerson failed to publish further work), referred to by Appel in 1941 (2), in which he showed granuloma formation at the site of injection of a sarcoid spleen extract in sarcoid patients. It was Siltzbach, however, who pioneered the universal application of the test (3), set standards to be met by satisfactory test suspensions (4), elaborated with his coworkers techniques to reduce to a minimum all possible causes of faulty preparation which might result in "false positive" responses, and established an international cooperative program which has become the model for validation of potentially active test material (5).

Ever since it was first described the Kveim-Siltzbach test has intrigued, tantalized and puzzled the medical world; intrigued because of the unique form the test takes, tantalized because of the repeated failure to identify the active principle involved, and puzzled because all efforts to define the nature of the Kveim-Siltzbach reaction have been unsuccessful. Nevertheless the cumulative experience of over two decades has resulted in a wide acceptance of the test as a reliable and clinically useful aid to diagnosis and it now deservedly enjoys the status of a landmark in the history of sarcoidosis. It is generally agreed that the test is a specific recognition system but debate continues in some quarters as to whether the factors it recognizes are exclusive to sarcoidosis or are capable of occurring in other diseases. The term "selectivity" as opposed to "specificity" has been advocated (6), since "specific" can have implications either in the sense of being related to a specific causal agent or in the statistical sense that a higher proportion of patients with active sarcoidosis react positively to the test whereas those with other diseases rarely do. The specificity in the statistical sense, with validated test

From the Department of Medicine, Royal Infirmary, Edinburgh.

substances which fulfill the Siltzbach criteria, has been amply demonstrated (7). Until it can be shown that an as yet unidentified agent uniquely causes sarcoidosis the term 'selectivity' leaves open the question of the reasons for the statistical association.

The finding of the active principle in sarcoid tissues which is responsible for a positive Kveim-Siltzbach test would, without doubt, add a new dimension to understanding the nature of the test and, one hopes, would bring closer the identification of the precise etiology of sarcoidosis. Chemical analysis has strongly suggested that it is a protein and the fact that testing with subcellular fractions has shown reactivity with nuclear, mitochondrial, and microsomal fractions but not with submicrosomal residue supports the view that the active principle is particulate and probably resides in the membrane components of sarcoid tissue cells (7). An exciting prospect in further determination of the provocative agent is the demonstration by meticulous work in mice that a possible transmissible agent in sarcoidosis is inactivated if the homogenates used in transmission studies are prepared from slow-frozen human sarcoid tissue stored at minus 20°C or are irradiated by ^{60}Co, conditions under which valid Kveim-Siltzbach test suspensions retain activity (6). Thus the search for the provoking factor may well be passing from the field of expertise of the initiated clinician and the experimental pathologist to that of the histochemist.

Effective Kveim-Siltzbach test suspensions must meet two basic criteria (4). They must have levels of sensitivity which can identify 60% or more of patients with sarcoidosis and they must have a level of specificity which excludes all but 2 to 3 percent of nonsarcoid subjects. It goes without saying that the sarcoid tissue used in preparation must be free from transmissible disease and in this context the donor certainly must be negative for Australia (B hepatitis) antigen. Unsatisfactory suspensions which did not fulfill the basic prerequisites either because they were too weak to detect sarcoidosis in a sufficiently high percentage of cases or reacted quite haphazardly in provoking granulomas in both sarcoid and nonsarcoid patients have been the source of some contention in the history of the test, particularly during the phase of critical appraisal of its clinical value. It is conceivable, however, that future observations with unsatisfactory test material may yield useful information in relation to knowledge of the genesis of intracutaneous granuloma formation—especially if the biochemist can identify the provocative agent in clinically acceptable suspensions. Similarly the explanation of why some initially effective suspensions should suddenly lose sensitivity or specificity (5) may provide a fruitful area of study at biochemical or immunologic level. Disparity between batch efficacy may, as Siltzbach has suggested, be explained by the fact that part of a sarcoid tissue need not represent the whole in terms of ability to yield a satisfactory test suspension (5). Again this is a possible field for exploration. Finally the fact that some patients with unequivocal clinical and histologic sarcoidosis fail to react positively to testing with several validated suspensions from different sources deserves further study, probably along immunologic lines. The Kveim-Siltzbach test which, despite several challenges, has retained its distinctive place in the diagnosis of sarcoidosis (6) has also disclosed a number of fascinating unsolved problems and pointed to areas of study with major potential in the further understanding of granulomagenesis. It may be that inconsistent and clinically unacceptable suspensions may merit as much study in the future as those meeting the criteria for diagnostic use.

To some extent Kveim and Siltzbach have been to sarcoidosis what Fleming and Florey were to penicillin. Kveim, after making his original observation, did not feature at all prominently in further investigative medicine. Siltzbach, taking up the torch, has catalyzed research activity into all aspects of the sarcoid process. The medical world has been singularly fortunate in the fusion of interest, inventiveness and originality of these two researchers whose work has firmly established the Kveim-Siltzbach test not only as the ultimate in diagnostic precision but as an invaluable tool in the continued investigation of the many unsolved problems in the etiology and pathogenesis of sarcoidosis.

References

1. Kveim, A.: En ny og specifikk kutan-reaksjon ved Boecks sarcoid, Nord Med 9:169, 1941.
2. Scadding, J. G.: The Kveim Reaction. In *Sarcoidosis*. Eyre and Spottiswoode, London 1967, p. 385.
3. Siltzbach, L. E.: An International Kveim Test Study, Acta Med Scand 176 (suppl 425):178, 1964.
4. Siltzbach, L. E.: Significance and Specificity of the Kveim Reaction, Acta Med Scand 176 (suppl 425):74, 1964.
5. Siltzbach, L. E.: Qualities and Behaviour of Satisfactory Kveim Suspensions. In *Seventh International Conference on Sarcoidosis and Other Granulomatous Disorders*, Edited by L. E. Siltzbach. The New York Academy of Sciences, New York 1976, p 665.
6. Mitchell, D. N. and Scadding, J. G.: Sarcoidosis, Am Rev Resp Dis 110:774, 1974.
7. Douglas, A. C., Wallace, A., Clark, J, Stephens, J. H., Smith, I. E., and Allan, N. C.: The Edinburgh Spleen: Source of a Validated Kveim-Siltzbach Test Material. In *Seventh International Conference on Sarcoidosis and Other Granulomatous Disorders*, Edited by L. E. Siltzbach. The New York Academy of Sciences, New York 1976, p. 670.
8. Douglas, A. C.: The Kveim Test and Its Practical Significance, Scand J Resp Dis Suppl 80:61, 1972.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Manifestations Radio-Cliniques et Physiopathologiques des Localisations Mediastino-Pulmonaires de la Sarcoidose

J. TURIAF

Reconnues pour la première fois par Kuznitzky et Bittorf les localisations médiastino-pulmonaires dominent la pathologie de la sarcoïdose. Solitaires ou associées à d'autres atteintes viscérales, elles sont présentes selon les statistiques dans 84 à 90% des cas pour une moyenne générale de 92% (James et al). Nous les avons notées dans 538, soit 96% des 562 cas qui composent notre série. L'aspect radiologique de la sarcoïdose médiastino-pulmonaire exprime assez fidèlement et chronologiquement son évolution en trois stades. Les adénopathies médiastinales solitaires représentent la période initiale ou stade I. L'infiltration parenchymateuse avec ou sans adénopathies médiastinales associées un état plus évolué: c'est le stade II. La fibrose pulmonaire, avec ou sans emphysème, mais dans tous les cas sans adénopathie accompagnatrice est la période terminale ou stade III.

Stade I ou d'adénopathies Médiastinales Solitaires

La fréquence des adénopathies médiastinales solitaires de la sarcoïdose chiffre 25 à 64% des cas selon les auteurs, avec une moyenne générale se situant autour de 50% (James et al). Elle chiffre 40% dans notre statistique. Ces adénopathies sont fréquemment reconnues fortuitement à l'examen radiologique de dépistage systématique. Elles siègent électivement dans les espaces interbronchiques et la face latérale droite de la trachée. Elles sont dans la plupart des cas bilatérales, rarement unilatérales et très fréquemment mais non nécessairement symétriquement développées. Les adénopathies médiastinales de la sarcoïdose sont volumineuses et aisément reconnaissables sur les téléradiographies et les tomographies. Elles s'y inscrivent à la manière de tumeurs homogènes, arrondies ou ovalaires à grand axe vertical, aux limites externes convexes, bien tracées, franchement soulignées par une ou plusieurs incisures. Elles ne provoquent, ni compression, ni refoulement des organes médiastinaux adjacents.

Ces adénopathies sont, malgré leur apparente monstruosité, des manifestations bénignes. Quand elles évoluent spontanément vers la résolution, elles ne récidivent que très exceptionnellement. La guérison totale et définitive est obtenue selon des pourcentage qui varient de 35 à 90% selon les statistiques, avec une moyenne générale de 65% (James et al). Nous avons obtenu parmi 70 cas de sarcoïdose au stade I, que nous avons pu suivre pendant au moins 5 ans, qu'au total 59 cas, soit 84% ont abouti à la guérison définitive dont 48 spontanément soit 68% et 11 soit 16% sous corticostéroïdes, tandis que 11 cas soit 16% (Tableau I) ont évolué vers la chronicité et l'invétération sans

From the Hospital Bichat, 170 Boulevard Ney, Paris.

TABLEAU I

Evolution de la Sarcoidose Mediastino-Pulmonaire au Stade I

	Stade I: 70 cas			
	M	%	M	%
Guérison spontanée	48 cas	68,5 %	*59 cas*	84 %
Guérison après traitement	11 cas	15,7 %		
Passage à la chronicité malgré le traitement	11 cas	15,7 %	*11 cas*	16 %

extension dans les poumons des atteintes sarcoïdiennes. Nous avons proposé de désigner cette variété de la maladie par sarcoïdose médiastinale fixée au Stade I.

Stade II ou Stade d'infiltration Pulmonaire

Les images radiologiques de la sarcoïdose pulmonaire au stade II traduisent l'infiltration diffuse du parenchyme par les granulomes sarcoïdiens. La fréquence de cet aspect de la maladie s'inscrit selon les auteurs entre 17 et 54% pour une moyenne générale de 29% (James et al). Dans notre récente statistique personnelle (1975) se chiffre 54%.

Signes cliniques. De même qu'au stade I, il n'y a ni symptôme fonctionnel, ni signe physique, ni altération de l'état général.

Signes radiographiques. Deux grands aspects représentent la sarcoïdose pulmonaire au stade II: l'association des images ganglio-médiastinales avec des opacités parenchymateuses; les images d'infiltration pulmonaire sans opacité médiastinale associée. Il est pratiquement assuré que ces deux modes de représentation de la sarcoïdose se succèdent et que l'infiltration pulmonaire ne se développe pas d'emblée et solitairement à l'exclusion des atteintes médiastino-ganglionnaires.

Les images de l'atteinte parenchymateuse du stade II sont habituellement bilatérales et rapidement généralisées. Elles débutent souvent dans les aires moyennes juxtahilaires ou sous apexiennes, puis s'étendent à la totalité des deux champs pulmonaires à l'exception de l'extrême sommet. Dans quelques cas exceptionnels, elles sont initialement représentées par un petit infiltrat unilatéral, à limites floues, d'aspect floconneux; dans d'autres par une plage unique bien circonscrite d'aspect réticulo-nodulaire.

Associées ou non aux adénopathies médiastinales, ces images des atteintes pulmonaires de la sarcoïdose peuvent être classées en deux grands types: les images nodulaires, les plus fréquemment notées, et les images en placards infiltratifs.

Les images nodulaires existent deux variétés. Les images micronodulaires sont composées d'une multitude de granulations de 1 à 3 mm de diamètre, de la grosseur d'un grain de mil, qui couvrent à la manière d'un fin semis la totalité des deux champs pulmonaires à l'exclusion de l'apex et d'une mince bande de parenchyme sus-diaphragmatique. Les images macronodulaires, les plus fréquemment rencontrées, sont représentées par la présence dans les deux champs pulmonaires de nodules de tailles variées de 3 à 5 ou 6 mm, moyennement opaques aux limites floues et irrégulières. Ces formations sont fréquemment reliées entre elles par des trainées linéaires réalisant l'image reticulo-nodulaire dont le dessin rappelle grossièrement celui d'un filet aux mailles inégales. Dans d'assez nombreux cas, les nodules opaques s'agglutinent les uns aux autres, formant par places de véritables nappes infiltratives.

Les images en plages infiltratives moins fréquentes que les images nodulaires consistent en de vastes infiltrats hétérogènes à contours imprécis de faible ou de moyenne densité qui siègent n'importe où dans les poumons mais affectionnent pour débuter les aires sous apicales et axillaires.

D'autres images, à vrai dire fort rares, appartiennent au stade II de la sarcoïdose: petit infiltrat solitaire unilatéral, sous apexien, d'aspect nuageux suggérant un foyer tuberculeux, plage réticulo-nodulaire unique bien circonscrite; boules rondes opaques siégeant dans les bases et les secteurs moyens, évoquant le classique lâcher de ballons du cancer secondaire du poumon. Ces diverses images s'observent à la phase initiale du stade II.

Evolution. La sarcoïdose pulmonaire au stade II évolue vers l'effacement des images pathologiques, selon les auteurs, entre 17 et 79% des cas pour une moyenne générale de 49% (James et al). Nous avons observé cette éventualité dans 63 soit 64,4% des 98 cas qui composent notre série (Tab. II). De même que pour stade I, il convient de distinguer dans ce taux global, les cas dans lesquels la guérison est intervenue spontanément qui sont au nombre de 17 soit 17,5% de ceux dans lesquels elle a été obtenue par le traitement aux corticostéroïdes et qui forment un groupe de 46 cas, soit 47% (Tableau II).

Rechutes et Récidives. Les rechutes et récidives ne se produisent pas en cas de guérison spontanée. Nous les avons notées dans 20, soit 20,5% des cas qui avaient subi le traitement cortisonique pendant deux ans. Elles se déclarent autour du 3 Eme mois qui suitl'interruption de la cure, exceptionnellement après 6 mois. Elles exigent pour être éliminées en toute sécurité une nouvelle cure de corticostéroïdes de un à deux ans en moyenne.

Résistance Relative aux Cortico-Stéroïdes: La sarcoïdose pulmonaire au stade II ne manifeste jamais d'irréductibilité totale envers les corticostéroïdes. Mais il se produit dans certains cas en cours de traitement un phénomène qui représente une sorte de résistance relative à ces médicaments. Nous l'avons noté dans 15 cas soit 15,2% de notre statistique. Tandis que

TABLEAU II

Evolution de la Sarcoidose Mediastino-Pulmonaire au Stade II

	98 cas			
	n	%	n	%
Guérison spontanée	17	17,5	63	64,4
Guérison sous corticostéroides	46	47		
Rechutes	20	20.5	35	35,7
Résistance relative aux corticostéroides	15	15.2		

l'effacement des images pathologiques est obtenue dans les délais habituels et que la posologie quotidienne initialement appliquée a été progressivement diminuée, se situant entre 5 et 7 mg de Prednisone par exemple, la rechute s'amorce sur les clichés thoraciques. Il convient dès lors d'augmenter légèrement de 3 à 5 mg la posologie du médicament pour provoquer la disparition des images, et chercher par tâtonnement la posologie minimale qui en assure l'effacement en permanence. Le traitement devra dès lors être maintenu inchangé dans la plupart des cas pendant de nombreuses années pour obtenir la guérison. Nous avons proposé de désigner cette variété de sarcoïdose par sarcoïdose pulmonaire partiellement cortisono-résistante.

Stade III de la Sarcoïdose pulmonaire. Cet aspect de la sarcoïdose pulmonaire correspond à la transformation fibreuse des granulomes sarcoïdiens et le développement de lésions d'emphysème mutilant. C'est pourquoi il est appelé stade de fibrose ou de scléro-emphysème. Il intervient tardivement après 15, 20 ans ou d'avantage d'évolution de la sarcoïdose. La fréquence de la sarcoïdose au state III varie selon les auteurs entre 4 et 33% des cas, avec une moyenne générale de 12% (James et al). Elle chiffre 6.1% dans notre statistique.

Signes cliniques. La sarcoïdose au stade III se manifeste fréquemment par des signes fonctionnels: dyspnée, toux et parfois expectoration muqueuse ou muco-purulente. Sauf dans certaines variétés rares, il n'y a pas d'atteinte de l'état général. L'examen somatique objective parfois des râles bronchiques, et/ou des foyers circonscrits de râles de soucrépitants, mais rarement de vastes plages de râles crépitants suggérant la fibrose interstitielle diffuse. L'hippocratisme digital est inhabituel.

Témoignages radiographiques. Ils sont dispersés dans les deux champs pulmonaires. Les adénopathies médiastinales sont absentes.

Les images pulmonaire revêtent à ce stade trois aspects principaux:

Images réticulo-nodulaires densifiées sont composées de gros nodules très denses, de taille et d'opacité inégales, irrégulièrement dispersés dans les deux champs avec tantôt une prédominance sous claviculaire, tantôt une confluence accrue juxta-médiastinale. Les nodules sont reliés entre eux par d'épaisses travées opaques. Dans quelques cas, des formations microkystiques se dessinent nettement entre les nodules fibreux réalisant l'aspect classique en "rayon de miel." Des plages rétractées d'opacité parenchymateuse accrue avec attraction des plans adjacents soulignent parfois vigoureusement la fibrose.

Images de condensation et de blocs fibreux circonscrits. Ces aspects sont les plus fréquemment notés. Les blocs fibreux ont l'aspect de masses ligneuses et rétractées d'opacité très dense, mais hétérogène, aux limites irrégulières et anfractueuses, d'où partent des prolongements rameux dans le parenchyme avoisinant. Ces formations se développent dans les régions juxta-hilaires réalisant parfois de véritables masses pseudo-tumorales bordant de chaque côté le médiastin.

Images de cavités et d'emphysème. Elles sont dans tous les cas associées aux images de fibrose. Les images cavitaires se développent dans le sein des masses fibreuses. Elles représentent tantôt de vraies cavités nécrotiques intrafocales par thrombose vasculaire spécifiquement sarcoïdienne, tantôt des bulles d'emphysème obstructif, conséquence de sténoses bronchiolaires de même origine. Ces cavités habituellement sèches ne possèdent pas d'aptitude à l'infection bactérienne par les pyogènes et le B. K. mais sont fréquemment le siège de la prolifération active d'Aspergillus fumigatus.

Les images d'emphysème péri ou juxta-focal se cantonnent parfois à la périphérie des foyers de fibrose en petites plages circonscrites. Mais elles occupent fréquemment de vastes fractions du parenchyme pulmonaire autour et bien au delà des blocs et placards de fibrose rétractile. Il s'agit d'emphysème destructif provoqué par les lésions mutilantes de la sarcoïdose du parenchyme.

Evolution: Abandonnée à elle-même la sarcoïdose pulmonaire au stade III ne subit qu'exceptionnellement une stabilisation spontanée au prix d'une insuffisance respiratoire fonctionnelle tolérable. Elle évolue plus fréquemment vers l'insuffisance respiratoire progressive qui entraine la mort en quelques années dansl'asphyxie et le coeur pulmonaire chronique. Le traitement ininterrompu par les corticostéroïdes est capable de stabiliser la maladie. Nous avons observé cette éventualité dans 3 de nos 30 cas soit 10%. Divers auteurs font état de guérison selon des pourcentages qui varient de 10 à 48% (James et al). Nous estimons qu'il ne s'agit pas de guérison véritable car des témoignages radiographiques indélébiles et de graves atteintes des grands paramètres de la fonction respiratoire persistent. Dans la plupart des cas, 90% de notre série, le traitement doit être indéfiniment maintenu.

Complications: Elles sont dominées par le coeur pulmonaire chronique qui provoque la mort en raison de son irréductibilité ou à l'occasion d'un épisode aigu d'insuffisance respiratoire par infection bronchique accidentelle. Les hémoptysies, fréquemment mortelles par leur abondance ou leur répétition sont la conséquence de la prolifération d'Aspergillus fumigatus dans les cavités nécrotiques qui se développent dans les blocs de fibrose.

Localisations Bronchiques de la Sarcoïdose. Elles sont dans la majorité des cas cliniquement muettes. Des images radiographiques d'hypoventilation ou d'atélectasie en révèlent exceptionnellement l'existence. Elle sant parfois visibles en bronchoscopie dans les rares cas où elles provoquent le développement de proliférations endobronchiques verruqueuses souples et congestives, ou d'une sténose par épaississement inflammatoire ou rétraction cicatricielle d'une bronche souche ou segmentaire. La muqueuse bronchique est dans la plupart des cas d'aspect normal. Elle est parfois le siège, au voisinage des éperons, de plages hyperhémiées légèrement inflammatories. Malgré l'absence de modifications significatives, la biopsie des éperons révèle dans prês de 60% des cas la présence dans la muqueuse de formations folliculaires signant le diagnostic de sarcoïdose. Nous les avons trouvées dans 237 cas soit 58,4% parmi les 406 soumis à cet inventaire. A noter que les follicules sarcoïdiens sont retrouvés fréquemment dans la muqueuse bronchique après l'effacement des images radiographiques assurant, éventuellement de la sorte, le diagnostic rétrospectif de la sarcoïdose. Au stade III les granulomes sarcoïdiens développés dans l'adventice et dans l'épaisseur de la paroi bronchique provoquent à mesure de leur transformation fibreuse l'enserrement sténosant et la dislocation de l'armature fibroélastique et cartilagineuse des bronches. Il en résulte la formation de rétrécissements et d'ectasies bronchiolaires qui sont parfois visibles en bronchographie et toujours reconnaissables à l'examen microscopique des blocs fibreux.

Localisations Pleurales. Elles s'expriment habituellement par un épanchement, parfois de grande abondance, tantôt citrin, tantôt séro-hémorragique. Dans des cas plus rares, elles se traduisent par des épisodes récidivants de pleurite sèche ou de pleuro-péricardite à rechutes. Des placards localisés d'épaississement pleural avec symphyse notamment des culs-de-sac ont été signalés comme appartenant en toute sécurité à la pathologie de la sarcoïdose. L'atteinte de la plèvre peut être cliniquement et radiologiquement insaisissable, mais identifiable histologiquement sur prélèvement pleuro-pulmonaire pour biopsie à thorax ouvert.

Le pneumothorax est presque aussi rarement rencontré au cours de la sarcoïdose que les pleurésies. Il s'est produit dans 7 de nos 538 cas, soit 1,3%. Il est habituellement généralisé, plus rarement cloisonné. Il se déclare indifféremment aux stades II et III de la maladie. Il est bénin dans l'ensemble, bien qu'il soit parfois sujet à des rechutes. Il peut être mortel quand il intervient sur un état d'insuffisance respiratoire avec coeur pulmonaire chronique.

Calcifications Médiastino-Pulmonaires de la Sarcoïdose.

Elles sont l'apanage de la sarcoïdose ancienne et vieillie. Nous les avons reconnues dans 8% des cas. Elles siègent tantôt dans le sein ou à la périphérie d'adénopathies médiastinales qui datent de plusieurs années, tantôt en plein parenchyme pulmonaire, dans les blocs fibreux et les plages de sclérose, tantôt enfin en simultanéité dans le médiastin et dans les poumons. Quand elles siègent dans les anciennes adénopathies, elle offrent l'aspect de gros nodules irréguliers, d'une opacité pierreuse, encombrant par leur nombre parfois très grand l'espace médiastinal. Quand elles se développent à la périphérie des masses ganglionnaires, elles sont dites en "couronne" ou en "coquille d'oeuf." Dans le parenchyme pulmonaire, les dépôts calcaires ont l'aspect de placards opaques ou de petites boules bariolant l'image des blocs fibreux. Dans des cas plus rares, elles ponctuent en "grains de plomb" une plage réticulo-nodulaire rétractée: "images discoïdes," "images en confettis." Toutes ces calcifications médiastinales et pulmonaires de la sarcoïdose sont bien tolérées dans l'ensemble.

Donnees de L'Exploration Fonctionnelle Respiratoire

La mesure des divers paramètres qui sont utilisés pour inventorier la fonction respiratoire permet: Au stade I d'identifier les atteintes parenchymateuses radiologiquement invisibles; au stade II de reconnaître et d'analyser les cas dans lesquels ces paramètres sont altérés, de faire avec une sécurité accrue la distinction entre stade II et stade III, pas toujours clairement inscrite sur les radiographies. Les données de l'exploration fonctionnelle respiratoire entrent en ligne de compte pour l'indication thérapeutique au stade I et pour la formulation du pronostic aux stades II et III.

Au stade I d'adénopathies médiastinales solitaires, sans atteinte parenchymateuse radiologiquement visible, les altérations significatives de la fonction respiratoire sont absentes dans près de 80% des cas. Quand elles sont présentes, elles sont habituellement discrètes et dissociées. Parmi 20 cas que nous avons très récemment inventoriés à cette période de la maladie, la valeur moyenne de la CPT est normale. La présence d'un syndrôme restrictif est notée dans 2 cas, soit 10%, l'augmentation du rapport VR/CPT audessus de 30% dans 1 cas soit 5%, 1a diminution du rapport VEMS/CV au dessous de 70% dans 1 cas, soit 5%, tandis que la résistance pulmonaire expiratoire totale est augmentée dans 2 cas, soit 10%, et la moyenne générale du rapport compliance effective/CPT n'est pas altérée de manière significative. L'index de distribution de l'air est accru dans 2 cas, soit 10%. La valeur de la capacité de diffusion du CO (DLCO) rapportée à la surface corporelle et à la surface alvéolaire s'est montrée légèrement diminuée dans tous les cas. Le facteur de membrane (DM) seul était altéré, à l'exception d'1 cas, soit 5%, dans lequel le volume capillaire (Qc) l'était également.

Au stade II d'infiltration granulomateuse, avec ou sans adénopathie médiastinale d'addition, mais sans fibrose, l'exploration fonctionnelle respiratoire peut être considérée comme normale dans 50% des cas. Elle a été effectuée chez 50 sujets. La valeur moyenne de la CPT est normale. Un syndrôme restrictif est présent dans 5 cas, soit 10%; l'augmentation du rapport VR/CPT dans 16 cas, soit 32%; la diminution du rapport VEMS/CV dans 7 cas, soit 14%, et l'augmentation de la résistance expiratoire pulmonaire totale dans 10% des cas. La moyenne générale du rapport Compliance Effective/CPT est normale de même qu'au stade I. L'indice de distribution de l'air est augmenté dans 7% des cas. Mesurée chez les sujets au stade II selon les mêmes méthodes qu'au stade I, la capacité de diffusion du CO s'est montrée diminuée dans tous les cas, sans différence significative avec le stade I. L'amoindrissement porte isolément sur DM, à l'exception de 11% des cas dans lesquels le volume capillaire Qc est aussi diminué.

Au stade III de la sarcoïdose pulmonaire, les atteintes des diverses composantes de la fonction respiratoire sont beaucoup plus fréquentes et sévères qu'aux stades I et II. Elles y sont présentes dans tous les cas. Dix sujets ont été soumis à l'inventaire respiratoire. La valeur moyenne de la CPT est diminuée. Le rapport VR/CPT est franchement élevé dans 5 cas, soit 50%. Il en est de même pour le rapport de Tiffeneau, VEMS/CV, dans 5 cas sur 10, et de la résistance expiratoire pulmonaire totale dans 8 cas sur 10. La moyenne des valeurs du rapport Compliance Effective/CPT est augmentée. L'indice de distribution de l'air est accru dans 60% des cas. L'amoindrissement de DLCO est présent avec altération de DM dans tous les cas avec jour 34% d'entre eux la diminution de Qc. Des désordres atteignant les gaz et l'équilibre acide-base du sang mesurés au repos sont fréquemment notés. Chez un groupe de 10 sujets il a été constaté: absence d'anomalie: 4 cas; hypoxémienormocapnie: 8 cas; hypoxémie-hypocapnie: 2 cas; hypoxémie-hypercapnie: 2 cas.

En résumé aux stades I et II l'atteinte de la fonction respiratoire est discrète et dissociée. Au stade III elle est sévère, témoignant notamment de la réalité des lésions bronchiolaires et du lit capillaire de poumon.

Evolution et Pronostic Général des Localisations Mediastinales et Pulmonaires de la Sarcoïdose.

Les atteintes médiastino-pulmonaires évoluent au cours de la sarcoïdose pour leur propre compte en toute indépendance des autres localisations. Bien plus, les adénopathies médiastinales et les infiltrations parenchymateuses ne possèdent pas dans tous les cas des destinées superposables. Il y a maintes fois dissociation dans leur évolution. Ailleurs l'effacement des images pathologiques ne coïncide pas nécessairement avec la suppression des troubles de la fonction respiratoire. Cette notion s'applique essentiellement au stade II. En effet, au stade I de la malade, la quasi totalité des atteintes de la fonction respiratoire disparaissent en simultanéité avec la résolution des adénopathies médiastinales. Au stade II, les troubles de la fonction respiratoire persistent dans environ 50% des cas, en partie ou en totalité après l'effacement spontané ou thérapeutique des images radiologiques. Dans 26 cas de sarcoïdose dans lesquels les infiltrations pulmonaires coexistaient avec des altérations de la fonction respiratoire, la suppression simultanée des stigmates radiologiques et des désordres de la fonction respiratoire a été obtenue dans 13 cas tandis que dans les 13 autres cas les atteintes fonctionnelles ont persisté malgré l'effacement total et définitif des images pulmonaires. Au stade III, les désordres fonctionnels demeurent malgré le traitement ainsi que l'essentiel des aspects radiologiques de fibrose.

Le pronostic global de la sarcoïdose médiastino-pulmonaire évalué dans 198 cas sur les données de la radiographie du thorax, sans distinction du stade évolutif, chiffre à 65% les cas qui évoluent vers la guérison et à 35% ceux qui demeurent inaccessibles au traitement (Tab. III). Mais cette évaluation globale ne convient pas pour l'énoncé du pronostic réel qui varie selon le stade où la maladie est identifiée.

Au stade I, elle possède un pronostic particulièrement bénin, la guérison définitive intervient dans 84% des cas, le reste, 16% versant dans

TABLEAU III

Pronostic Selon le Stade de la Sarcoïdose

	Guérison %	Récidive Passage chronicité %
Stade I	84	16
Stade II	64	36
Stade III	10	90

l'invétération des adénopathies qui demeurent inchangées. Le développement de calcifications ne menace ni localement, ni ailleurs.

Au stade II, la maladie doit aussi être tenue pour bénigne. La guérison est définitivement obtenue dans 64% des cas. Les autres, soit 36% se répartissent entre les rechutes et la résistance relative aux corticostéroïdes. Ils peuvent être contrôlés par un traitement ininterrompu qui s'oppose au développement de la fibrose pulmonaire.

Au stade III, la sarcoïdose représente un état de haute gravité. Le traitement à cette période ne permet d'obtenir l'extinction définitive de l'activité de la maladie que dans un petit nombre de cas: 10 %, dans notre statistique. Des complications redoutables menacent le pronostic: hémoptysies mortelles, coeur pulmonaire irréductible, épisodes aigus de détresse respiratoire sur le fond d'insuffisance respiratoire chronique.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Neurosarcoidosis or Granulomatous Angiitis: A Problem of Definition

H. URICH

"Not all that glitters is sarcoidosis," *D. G. James*

Neurosarcoidosis may be defined as the involvement of the nervous system, central or peripheral, in multisystemic sarcoidosis. This definition although apparently simple and self-evident, is open to several reservations. In the first place it preempts the still controversial question of the existence of isolated neurosarcoidosis, confined to the central nervous system (CNS). Furthermore it should include only those neurologic manifestations of the disease in which the nervous system is affected by the typical granulomatous process. The altered immunologic status of the patients may lead to neurologic complications such as opportunistic infections and perhaps immune complex disorders, but these are not part of neurosarcoidosis. As a corollary of this reservation we would have to exclude at present those neurologic manifestations in which we possess inadequate pathologic data, such as some of the peripheral syndromes or the transient cerebral symptoms in acute sarcoidosis. Finally, in accepting the presence of noncaseating epithelioid-cell granulomas as the hallmark of neurosarcoidosis, we must separate the disease clearly from other granulomatous conditions affecting the central nervous system.

The confusion between sarcoidosis and tuberculosis is now largely of historical interest, but some of the early cases of neurosarcoidosis were reported as examples of tuberculosis (1, 2). There is also little difficulty in differentiation of neurosarcoidosis from granulomatous conditions caused by other well-defined causative agents, such as coccidioidomycosis. There remains, however, a small, possibly heterogeneous, group of cases of obscure etiology known collectively by the name of granulomatous angiitis of the CNS. This condition, first described by Harbitz (3), named and defined by Cravioto and Feigin (4), was recently reveiwed by Kolodny et al (5) and by Nurick, Blackwood and Mair (6). It is a vasodestructive disorder, affecting both arteries and veins, characterized by necrosis of the vessel wall with a granulomatous, usually giant-cell, reaction, involving exclusively or predominantly the central nervous system. Its separation from neurosarcoidosis is not as clearcut as may appear from simple definitions. This is illustrated by the fact that the well-known case of Zollinger (7) is interpreted by some writers as neurosarcoidosis, by others as granulomatous angiitis.

The following, somewhat atypical case, may highlight some of the nosologic problems.

From the Institute of Pathology, The London Hospital, London, England.

Case Report

C. G., a 61-year-old West Indian man, was first seen in June 1975 at the Venereology Department as a contact of his wife who suffered from neurosyphilis (tabes dorsalis). Apart from being somewhat depressed, the patient was asymptomatic at the time. The only relevant history was that of yaws at the age of 17. On examination no abnormal physical signs were detected in any system. All serologic tests for syphilis were positive in the blood. The cerebrospinal fluid (CSF) contained 15 white cells per cmm and 95 mgms of protein per 100 ml, with a weakly positive mid-zone Lange curve (11122211). All tests for treponemal infection were negative in the cerebrospinal fluid. Since the patient was allergic to penicillin he was treated with a course of Cephaloridine 500 mg, 4 times daily by intramuscular injection for 17 days.

After the completion of his treatment he started having episodes of confusion, drowsiness, and ataxia. These symptoms gradually worsened and were associated with anorexia, weight loss, and impotence. On admission to hospital in October 1975 he had variable ataxia of his upper and lower limbs, inconsistent nystagmus, and extensor plantar responses. An air encephalogram showed some cortical atrophy confined to the frontal lobes, with normal ventricles. EEG showed slow wave activity. CSF contained 200mgms of protein/100ml, falling to 80 mg on a subsequent examination, otherwise no abnormality. Biochemical and hematologic investigations showed no abnormality except for a sickle cell trait.

He was readmitted in January 1976 with a chest infection. Despite vigorous treatment his condition deteriorated rapidly. He became more drowsy and unresponsive and died on February 4th.

Autopsy findings: The general findings were unremarkable except for bronchopneumonia, more severe in the right lung, and prostatic hypertrophy.

The brain weighed 1220 g and showed slight atrophy of the frontal lobes and superior parietal lobules. There was a thin film of subarachnoid blood over the convexity of both hemispheres and dense purpura over the base of the pons. The blood vessels appeared normal and free from atheroma. Coronal slices revealed extensive purpura throughout the brain. This was most marked in the brain stem (Fig. 1) and the white matter of the cerebellum but was also present in the inferior and medial parts of the frontal and temporal lobes, the centrum semiovale, the fornix, the thalamus and hypothalamus (Fig. 2).

Microscopically all lesions were associated with blood vessels and exhibited different patterns. Most of the lesions which appeared as purpuric spots macroscopically were in fact grossly dilated small veins (Fig. 3). These were most conspicuous in the brain stem and hippocampus, but were also present in the basal ganglia, thalamus, hypothalamus, and cerebellum. In some places, particularly in the pons, this venous dilatation was accompanied by frank hemorrhages. Several of the affected vessels showed fibrinoid necrosis of their walls, others showed variable degree of intimal fibrosis with partial or subtotal obliteration of the lumen (Fig. 4). The walls of some of the obliterated vessels were partially calcified (Fig. 5). In addition inflammatory lesions were associated with blood vessels, both arterioles and venules, though not necessarily the dilated or necrotic ones (Fig. 6). The inflammatory process consisted in some places of nonspecific lymphocytic cuffing, in others of a granulomatous reaction consisting of epithelioid cells with scanty, inconspicuous giant cells and an outer ring of lymphocytes (Fig. 7). These granulomas were relatively sparse and most abundant in the temporal lobes. Scanty perivascular granulomas were also found in the leptomeninges and in the roots of some of the cranial nerves (Fig. 8).

No granulomatous lesions were found in any other organs.

Discussion

The interpretation of these findings is difficult. In view of the positive serology neurosyphilis must be considered. However, the persistently negative treponemal tests in the CSF, the rapid deterioration of the patient's

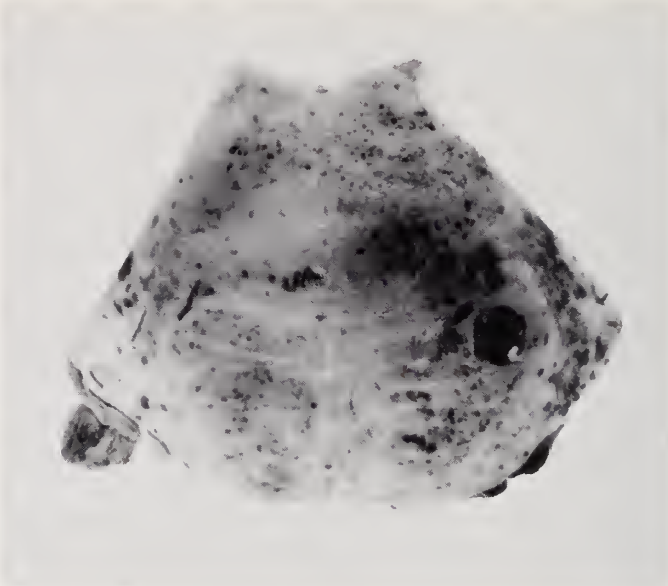

FIG. 1. Transverse section through the pons showing purpura consisting both of dilated vessels and hemorrhages (magnification × 2).

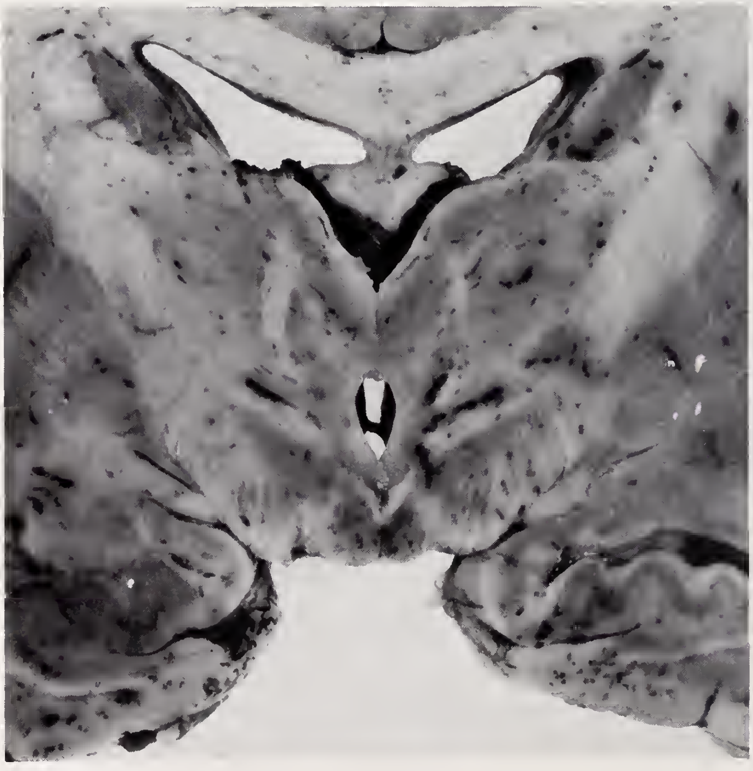

FIG. 2. Coronal section through anterior thalamus and adjacent structures showing dilated blood vessels (magnification × 2).

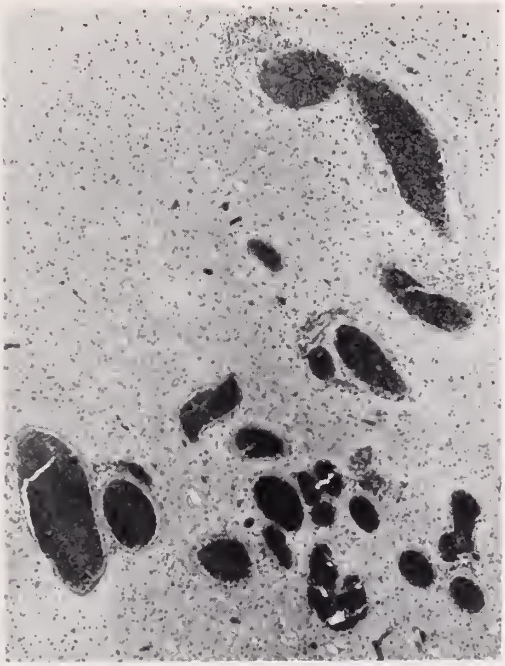

FIG. 3. Low-power view of temporal white matter showing dilated blood vessels and associated inflammatory lesion (H&E, magnification × 45).

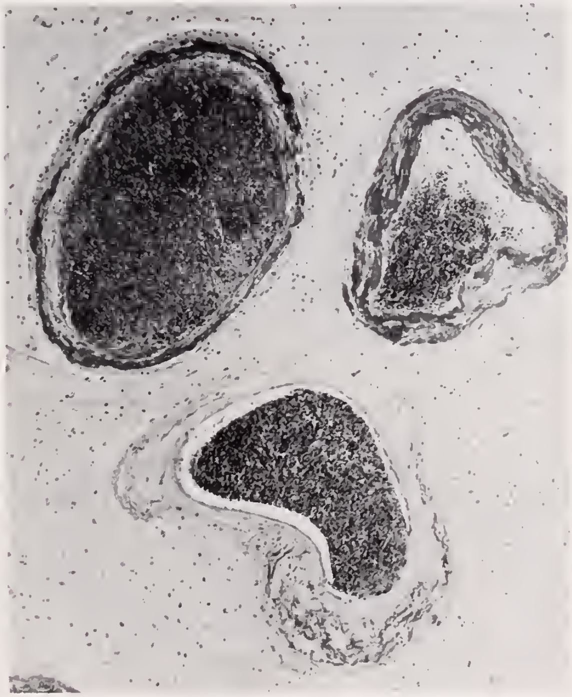

FIG. 4. Group of dilated blood vessels showing fibrinoid necrosis in vessel wall and intimal fibrosis (H&E, magnification × 75).

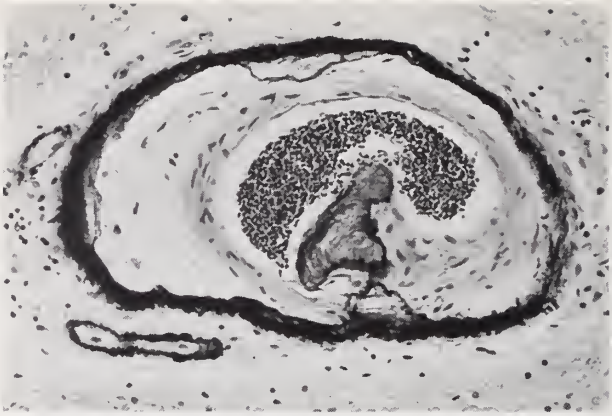

FIG. 5. Partially obliterated and calcified vessel in pons (H&E, magnification × 180).

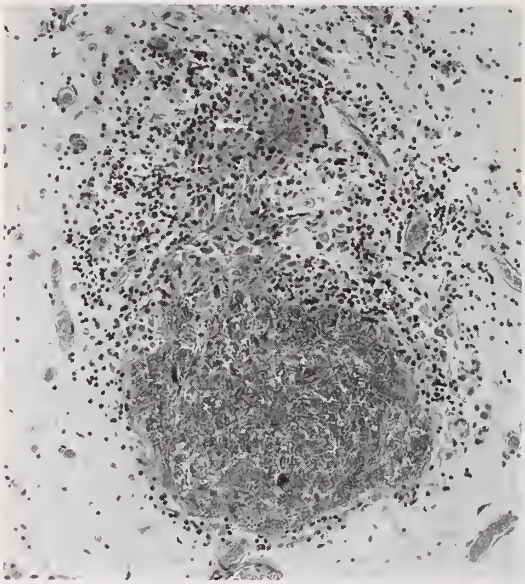

FIG. 6. Granulomatous lesion adjacent to dilated venule end eroding its wall (H&E, magnification × 135).

condition after adequate treatment, and the histologic appearances of the lesions totally unlike those of meningo-vascular syphilis, all render this diagnosis improbable. The noncaseating epithelioid-cell granulomas closely resembled those of sarcoidosis, yet their sparsity compared with the abundance of other vascular lesions and their total absence in other organs renders this diagnosis untenable. The case is therefore best classified as a variant of granulomatous angiitis of the CNS although it differs in some details from the previously reported ones. The dissociation between the necrotizing and granulomatous lesions was striking in the present case, while in most cases the granulomas form in close association with the necrotic segments of

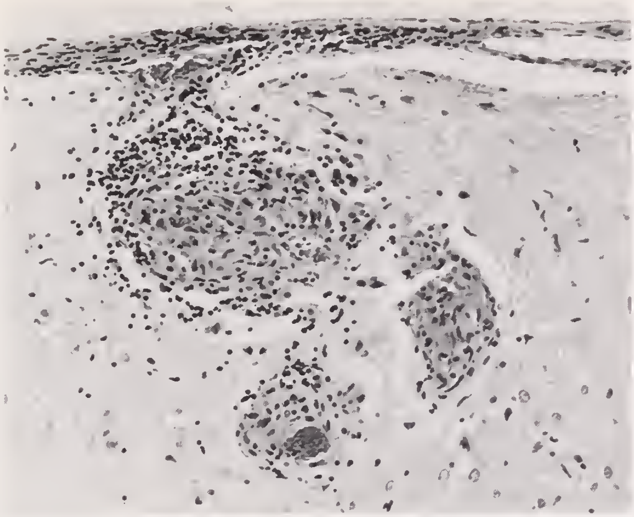

FIG. 7. Cluster of granulomas surrounding normal cortical blood vessels, also infiltration of leptomeninges (H&E, magnification × 180).

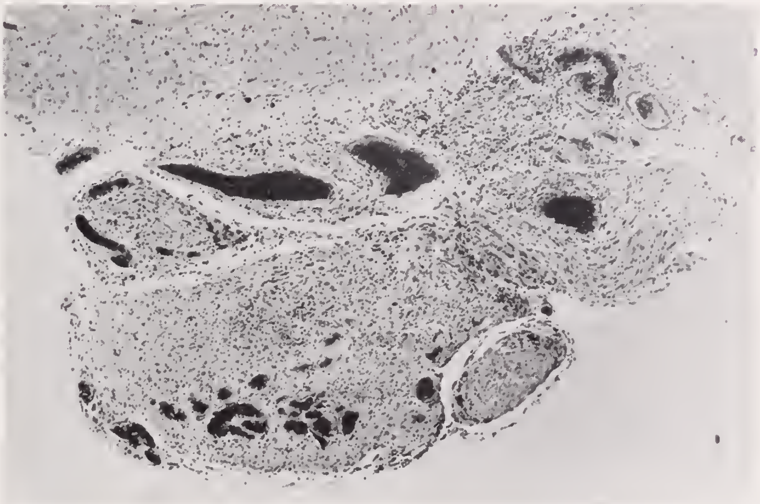

FIG. 8. Involvement of root of hypoglossal nerve in granulomatous mass (H&E, magnification × 60).

vessels. Giant cells, both of foreign body and of Langhans type are usually abundant and form the most conspicuous feature in the granulomas; in the present case they were exceptionally sparse. The vascular dilatation, reminiscent of a congenital telangiectatic malformation, was another unusual feature. Perhaps it was due to venous obstruction with expansion of the proximal radicles of obliterated venous channels, as in the phlebectasia described by Friede (8) as a residual lesion of venous thrombosis. Neoformation and proliferation of veins in the CNS have also been reported in a case of Eales' disease with neurologic involvement (9).

An attempt to differentiate granulomatous angiitis from other similar conditions was made by Kolodny et al (5) who defined it as a disease affecting arterioles and venules, principally in the CNS, associated with vascular necrosis and giant-cell granulomas, as opposed to sarcoidosis in which the lesions are extravascular, multisystemic and free from necrosis. This separation is, however, not as clearcut as the authors imply. While it is undoubtedly true that most granulomas in meningo-vascular sarcoidosis are adventitial, invasion and destruction of the vessel wall and partial or total obliteration of the lumen has been reported in several instances (7, 10–13). Even insistence on fibrinoid necrosis of the vessel wall does not rule out sarcoidosis as it has been recorded twice (10, 13). Admittedly it is a rare event, possibly an epiphenomenon not directly related to sarcoidosis, but its presence may create diagnostic difficulties.

As granulomatous angiitis is more likely to be a descriptive term than a nosologic entity, it is perfectly legitimate, if undesirable, to include in this category all cases of vasodestructive granulomatous lesions of the CNS irrespective of their associations. Maybe then, as Meyer et al (10) state, granulomatous angiitis may occur in the context of multisystemic sarcoidosis or be independent of it. This, however, would split neurosarcoidosis into two groups, those with and those without angiitis, a separation for which there appears to be no justification. There is thus a strong case for the exclusion of all cases of neurosarcoidosis from the class of granulomatous angiitis. Similarly, other cases with well-established associations with multisystemic diseases ought to be excluded, such as the second case of Newman and Wolf (14) which is a rare example of involvement of cerebral vessels in the allergic granulomatosis of Churg and Strauss (15).

Even with strictest criteria there remains a no-man's land in which the interpretation of findings is largely arbitrary. Two cases of granulomatous angiitis, the second patient of Cravioto and Feigin (4) and that of Peison and Padleckas (16) had extravascular granulomas in the viscera and could therefore be interpreted as atypical cases of sarcoidosis.

There is one further problem of a practical nature which frequently faces neuropathologists, that of a brain referred for examination with scanty clinical and pathological data. It may be asked whether in these circumstances a neuropathologist is ever justified in making the diagnosis of neurosarcoidosis. In my opinion, he is if presented with typical lesions which have now been adequately described, as these are not mimicked by other conditions. If the lesions deviate significantly from the recognized patterns he must reserve judgment.

In conclusion the following guidelines may be suggested:

1. Any case of meningo-vascular granulomatosis associated with multisystemic sarcoidosis is a case of neurosarcoidosis, even in the presence of some atypical features.
2. If multisystemic sarcoidosis is associated with involvement of the CNS by

a process not characterized by the formation of noncaseating epithelioid-cell granulomas, this should be interpreted as a neurologic complication and not as neurosarcoidosis.

3. A process characterized by a necrotizing vasculitis with a granulomatous reaction confined to the CNS or associated with a similar vasculitis in other organs is granulomatous angiitis of the CNS.
4. In examining an isolated brain only typical cases can be allocated to one category or the other; in other situations only a tentative diagnosis is possible.
5. A small group of unclassifiable cases will always remain.

Acknowledgments

The author is indebted to Dr. E. M. C. Dunlop and Professor D. W. Vere for the access to their clinical records and to Mr. H. J. Oliver for his technical assistance.

References

1. Strasman, —.: Ueber Eine Seltene, Sehr Chronische Verlaufsform Tuberkulöser Meningitis, Mitt Grenzgeb Med Chir 23:351–366, 1911.
2. Simons, A. and Merkel, H.: Zur Kenntnis der Chronischen Tuberkulösen Zerebrospinalmeningitis, Neurol Zentbl 36:258–277, 1917.
3. Harbitz, F.: Unknown Forms of Arteritis, with Special Reference to their Relation to Syphilitic Arteritis and Periarteritis Nodosa, Am J Med Sci 163:250–272, 1922.
4. Cravioto, H. and Feigin, I.: Noninfectious Granulomatous Angiitis with a Predilection for the Nervous System, Neurology (Minneap) 9:599–609, 1959.
5. Kolodny, E. H., Rebeiz, J. J., Caviness, V. S., Jr., and Richardson, E. P.: Granulomatous Angiitis of the Central Nervous System, Arch Neurol (Chicago) 19:510–524, 1968.
6. Nurick, S., Blackwood, W., and Mair, W. G. P.: Giant Cell Granulomatous Angiitis of the Central Nervous System, Brain, 95:133–142, 1972.
7. Zollinger, H. U.: Grosszellig-Granulomatöse Lymphangitis Cerebri (Morbus Boeck) Unter dem Bilde Einer Multiplen Sklerose Verlaufend, Virchows Arch (Pathol Anatom) 307:597–615, 1941.
8. Friede, R. L.: Residual Lesions of Infantile Cerebral Phlebothrombosis, Acta Neuropathol (Berlin) 22:319–332, 1972.
9. Dastur, D. K. and Singhal, B. S.: Eales' Disease with Neurological Involvement. Part 2: Pathology and Pathogenesis, J Neurol Sci 27:323–345, 1976.
10. Meyer, J. S., Foley, J. M. and Campagna-Pinto, D.: Granulomatous Angiitis of the Meninges in Sarcoidosis. Arch Neurol Psychiat (Chicago) 69:587–600, 1953.
11. Alajouanine, T., Bertrand, I., Degos, R., Contamin, F. and Escourolle, R.: Sarcoidose Ganglionnaire, Cutanée et Oculaire, avec Atteinte Secondaire Diffuse, Périphérique et Centrale, du Système Nerveux, Rev Neurol (Paris) 99:421–447, 1958.
12. Reske-Nielsen, E. and Harmsen, A.: Periangiitis and Panangiitis as a Manifestation of Sarcoidosis of the Brain, J Nerv Ment Dis 135:399–412, 1962.
13. Herring, A. B. and Urich, H.: Sarcoidosis of the Central Nervous System, J Neurol Sci 9:405–422, 1969.
14. Newman, W. and Wolf, A.: Non-infectious Granulomatous Angiitis Involving the Central Nervous System, Trans Am Neurol Assoc 77:114–117, 1952.
15. Churg, J. and Strauss, L.: Allergic Granulomatosis, Allergic Angiitis and Periarteritis Nodosa, Am J Path 27:277–301, 1951.
16. Peison, B. and Padleckas, R.: Granulomatous Angiitis of the Central Nervous System, Ill Med J 126:330–334, 1964.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Some Aspects of the Differential Diagnosis of Sarcoidosis

THOME G. VILLAR

Because the etiology of sarcoidosis is unknown, diagnosis must be based on the descriptive definition of the disease. The latest version was presented and discussed at the VII International Conference on Sarcoidosis and Other Granulomatous Diseases, held in New York in September 1975 under the presidency of Louis E. Siltzbach (1).

If the descriptive definition is not closely followed, other diseases besides sarcoidosis will to be lumped into the same group, and this may be disastrous in terms of treatment and results.

Many of the characteristics that make up the descriptive definition of sarcoidosis are common to many other diseases. The following we consider minor characteristics:

Multisystem Granulomatous Disorder: Hematogenous tuberculosis, histiocytosis X and Extrinsic Pulmonary Granulomatoses (EPG) (2–5) cause more or less widespread granulomas, impossible to distinguish from those of sarcoidosis on routine histology, in more than one organ or system. Some authors believe that multisystem distribution is an epiphenomenon of a particular type of reactivity and not directly related to the disease (7).

Affecting Young Adults: Tuberculosis, Hodgkins disease and eosinophilic granuloma frequently affect this age group.

Bilateral Hilar Lymphadenopathy (BHL): Many cases of EPG, some cases of miliary tuberculosis, and a few of Hodgkins disease present a radiologic picture of BHL. However, when BHL is associated with erythema nodosum or iritis, it is highly suggestive of sarcoidosis because this association rarely occurs in tuberculosis. BHL may very rarely be seen in primary or secondary malignancy.

Clinicoradiologic Findings Supported by Histologic Evidence of Widespread Noncaseating Epithelioid Cell Granulomas in More Than One Organ: There is no specificity in noncaseating epithelioid granulomas (8) as a granulomatous reaction differs only slightly with the cause (9) and can be found in tuberculosis, leprosy, syphilis, fungal infections, organic (Fig. 1) and inorganic inhaled particles, and malignant disease. The pathologist should make an exhaustive attempt to exclude the presence of bacteria, fungi, parasites or foreign particles within the granulomas that might be responsible for the lesions. In addition to routine polarized light microscopy (to exclude the presence of silica and other substances such as cement, synthetic fibers, wood particles and certain plastics), histochemical and incineration techniques, spectrography, microsound, and x-ray diffraction techniques (2, 3, 4, 5) should be used to exclude the presence of foreign matter within the

From the Department of Chest Diseases, Lisbon University Hospital, Lisbon, Portugal.

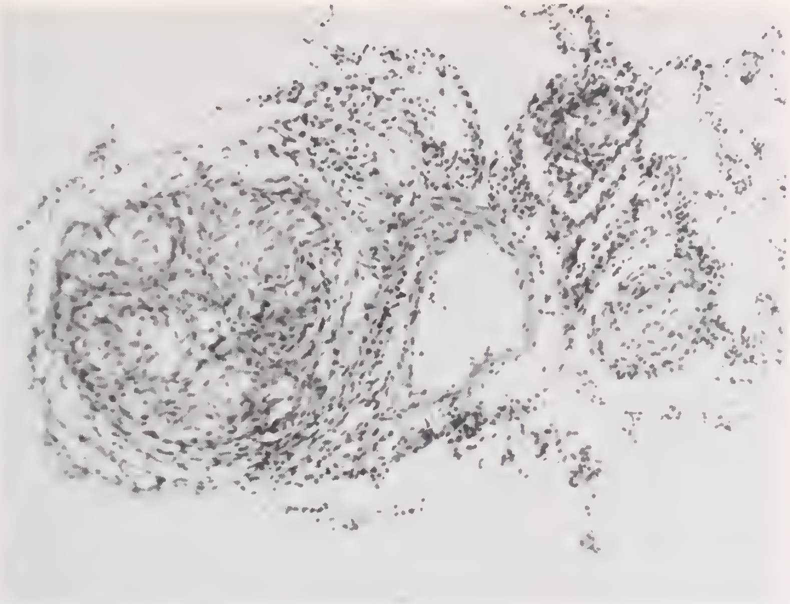

FIG. 1. Sarcoid-type epithelioid granuloma in an advanced cicatricial stage, with deposit of dark pigment that staining with cochineal red proved to be cork dust (lung biopsy from a patient with suberosis).

lesions. If living agents are suspected, the pathologic specimens should be submitted to bacteriologic, viral, and fungal studies to exclude these as causal agents. The site from which biopsies are taken is most important. Biopsy of demonstrable skin or glandular lesions or of affected lungs is generally the most reliable. Liver biopsy should only be considered when no other biopsy is available because of the tendency of the liver to form epithelioid granulomas, a fact most elegantly demonstrated by Pimentel in many different types of EPG (6).

Immunologic Features of Delayed-Type Hypersensitivity Depression: These suggest impaired cell-mediated immunity, and raised or abnormal immunoglobulins. Such features are frequently found in EPG, miliary tuberculosis, Hodgkins disease, and in lymphangitis carcinomatosa.

Course and Prognosis Correlation with the Mode of Onset: This correlation applies far more to EPG than to sarcoidosis in our experience, perhaps because we have seen relatively few cases of acute onset in sarcoidosis.

Corticosteroid Treatment: This relieves symptoms and suppresses inflammation and granuloma formation as in most of the diseases that simulate sarcoidosis.

Other characteristics of the descriptive definition of sarcoidosis are diagnostically more valid on the condition that they are carefully evaluated and can be considered major items for the diagnosis of sarcoidosis.

Disorder of Unknown Etiology: This is a fundamental item because it separates the disease or syndrome sarcoidosis from the various sarcoid-type reactions. The EPG seem to constitute one of the latter type of reactions that most closely simulates sarcoidosis. The patient's environmental and professional history should be exhaustively explored and possible correlations between exposure and disease thoroughly investigated. Consequently, the diagnosis of sarcoidosis will quite often be reached.

Skin or Eye Lesions: Although these lesions may also appear in tuberculosis, the aspect of the skin lesions is often quite characteristic. However, in our experience, lupus pernio of a finger was mistaken for a tuberculous spina ventosa; similarly, an angioma of the phalanx was classified as being sarcoidosic (Fig. 2, A and B). With the involvement of the uveal tract, particularly when associated with parotiditis in Heerfordt's syndrome, or when iridocyclitis is associated with BHL, the probabilities of the diagnosis of sarcoidosis are very high.

Possible Hypercalciuria with or without Hypercalcemia: Although hypercalcemia is a feature of many other diseases and, in Lisbon, was only detected in 28% of sarcoid patients, (10) hypercalciuria when appearing within the clinicoradiologic setting of sarcoidosis, is highly suggestive of sarcoidosis.

Diagnosis Supported by a Positive Kveim-Siltzbach Reaction: In our experience this is the most helpful item in the diagnosis of sarcoidosis. In our series we had 78% of positive reactions in sarcoidosis and no false-positive reaction (10). It is most important that highly selective antigens, be used, as less carefully prepared antigens give false-positive results or a higher percentage of false-negative results. Dr. Siltzbach, using antigens prepared in his laboratory exclusively, gets positive results in as high as 92% of his sarcoid patients. It is also important that all technical details be carefully observed in carrying out this reaction and that the biopsy histology of the reactive site be read by pathologists familiarized with sarcoidosis.

By assay which supports major and minor items of the descriptive definition with a careful histology of biopsy specimens taken from uncontroversial sites, and with carefully performed Kveim-Siltzbach reactions, using highly reliable antigens, the diagnosis of sarcoidosis can generally be made with a high degree of certainty. Since sarcoidosis is a radiologic finding, in 28% of the cases in our series (10), it seems proper to say a word on the radiologic differential diagnoses of the various stages of the thoracic manifestations of sarcoidosis.

Stage I: Bilateral hilar lymphadenopathy can be simulated by most dust diseases, both organic and inorganic, in which the hilar enlargement seems to be a sign of overloading of the lymphatic clearance mechanisms of the lungs (Fig. 3). This radiologic picture was found in 15% of the total of our cases of EPG, as against 38% in our sarcoidosis series. Eggshell calcifications, known to appear in EPG, and especially in silicosis, have also been reported in cases of "sarcoidosis," although in not all of them was it possible to evaluate the consistency of the diagnosis.

Tuberculous primary infection may on occasion lead to roentgen pictures of BHL. However bilateral hilar adenopathy shows general asymmetry and the clinical picture makes diagnosis easy.

This is not always the case when Hodgkins disease appears as BHL,

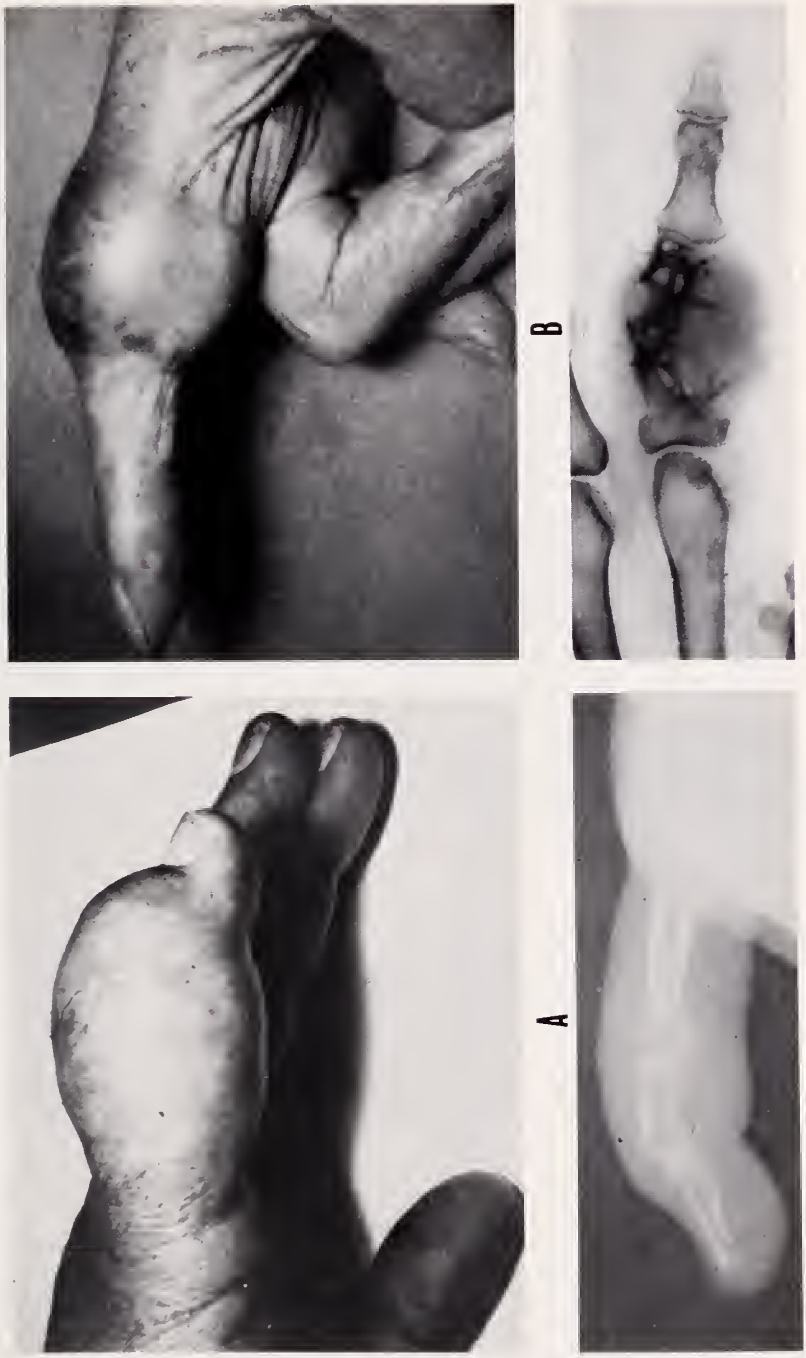

FIG. 2. "Blown-up" finger in a proved case of sarcoidosis and roentgenogram showing the changes in the bone (A). This case of lupus pernio was considered for some time to be a tuberculous spina ventosa. (B) Another finger simulating lupus pernio and the respective roentgenogram, in a patient with dermatomiositis and an angioma of the phalanx proved by amputation.

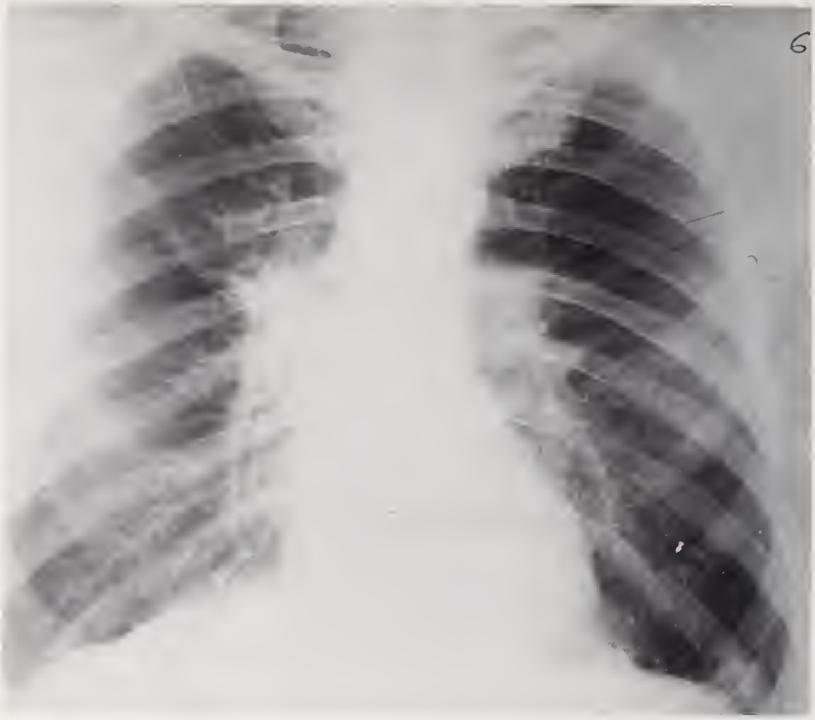

Fig. 3. Roentgenogram of the chest of a cabinetmaker who worked with exotic woods. Note the bilateral hilar enlargement and the fine nodular mottling irradiating from the hilae. Lung biopsy showed a pulmonary granulomatosis caused by wood dust which was found in the granulomas.

generally in young females with few or no symptoms. Some of these cases have been reffered to us as tuberculous primary infections and the full picture of the disease only appeared much later. Although the glands tend to come together and lose their individuality in Hodgkins disease, in one case this was not so, the glands were well defined, bilateral and fairly symmetrical as in sarcoidosis (Fig. 4). What led to the diagnosis of Hodgkins disease was the involvement of many groups of peripheral lymph nodes, which is most unusual in sarcoidosis.

In lymphosarcoma and metastatic carcinoma, hilar glandular enlargement is less symmetrical, the individual glands cannot be identified, their contours seem more invasive and they tend to encroach on the bronchial tree. This, however, was not the case in a patient with metastatic hyperneproma, clinically and radiologically undistinguishable from sarcoidosis and in which scalene node biopsy made the diagnosis (11).

Stage II: In the differential diagnosis of this stage of sarcoidosis (in which bilateral pulmonary infiltration is associated with enlarged hilar shadows that tend to disappear), miliary tuberculosis, EPG, malignancy and cardiovascular changes are the main groups of disease to be considered in arriving at a diagnosis.

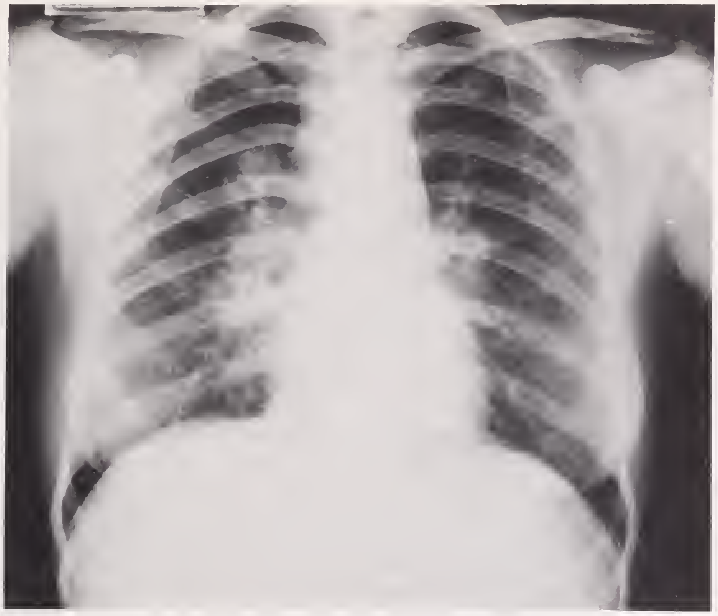

FIG. 4. Roentgenogram of the chest showing well-defined, symmetrical, bilateral hilar lymphadenopathy in a young asymptomatic woman. Peripheral lymph node biopsy showed Hodgkin's disease.

Miliary tuberculosis tends to present with few and uncharacteristic symptoms nowadays and not with the well-known characteristic clinical picture of former years. However, the distribution of the lesions is more uniform, the apices being more frequently involved, and the lesions tend to have hazy outlines and to show confluence.

Extrinsic Pulmonary Granulomatoses frequently simulate this stage of sarcoidosis and, unless a history of specific exposure is obtained, a purely radiologic diagnosis may prove difficult as the distribution and type of lesions are very similar. In cases where the patient is exposed to particles of high molecular weight, the high density of the individual lesions may put one on the right track.

In malignancy, both primary as in alveolar cell carcinoma or secondary as in lymphangitis carcinomatosa, each individual lesion is less well defined, the sizes differ and distribution is less symmetrical. This asymmetry is even more marked in relation to the hilar shadows which tend to increase instead of regress.

In the cardiovascular conditions that simulate this stage of sarcoidosis, the clinical picture generally sets one on the track of the diagnosis. Radiologically the distribution of the mottling predominant in the lower two-thirds of the lung fields, the hazy outlines of the individual components of the image, and the fact that hilar enlargement is a result of distended pulmonary arteries instead of enlarged hilar glands, should suggest the diagnosis.

Stage III: All fibrosing processes that can take place in the lungs have to be considered in the differential diagnosis of this stage of sarcoidosis. Not only those of known etiology such as tuberculosis, both organic and inorganic EPG, and fungal disease, but those of unknown etiology such as Histocytosis X, and particularly eosinophilic granuloma and cryptogenic fibrosing alveolitis, must be considered. This is where the diagnostic discernment of the physician is particularly important, and must be supported by all the bacteriologic, biochemical, immunologic, and accessory techniques available. In many of these cases not even lung biopsy can furnish complete proof of the nature of the disease because the morphologic findings are the result of an abandoned battleground.

It is in these cases that the newer techniques, such as the evaluation of the levels of the angiotensin-converting enzyme in the serum, may come to be of the greatest help, although this has yet to be tested in relation to the other granulomatoses.

In rare cases metastatic malignancy may give similar radiologic aspects but these are generally rapidly clarified.

It would seem that in many cases of sarcoidosis complete certainty in diagnosis is difficult to achieve. "The diagnosis of sarcoidosis is a statement of belief or knowledge that noncaseating epithelioid-cell tubercles, or their hyalinized remains, not due to other causes, are present in a number of affected organs or tissue" (12). However, the power of "belief" is necessarily greater in countries where the incidence of sarcoidosis is higher, while knowledge must necessarily prevail in those areas in which sarcoidosis is rare and where other diseases that frequently mimic sarcoidosis are still quite prevalent.

References

1. James, D. G., Turiaf, J., Hosoda, Y., Jones Williams, W., Israel, H. L., Douglas, A. C., and Siltzbach, L. E.: Description of Sarcoidosis: Report of the Subcommittee on Classification and Definition, Ann NY Acad Sc 278:742, 1976.
2. Pimentel, J. C. and Marques, A. P.: Vineyard Sprayer's Lung, Thorax 24:678, 1969.
3. Pimentel, J. C.: A Granulomatous Disease Caused by Bakelite. A Clinico-Pathologic and Experimental Study, Amer Rev Resp Dis 108:1303, 1973.
4. Pimentel, J. C. and Avila, R.: Respiratory Disease in Cork Workers (Suberosis) Thorax 28:409, 1973.
5. Pimentel, J. C., Avila, R., and Lourenço, A. G.: Respiratory Disease Caused by Synthetic Fibers. A New Occupational Disease, Thorax 30:204, 1975.
6. Pimentel, J. C. Liver Disease in Vineyard Sprayer's Lung, Gastroenterology 72:275, 1977.
7. Corda, M. and Paroli, M.: Quadri polmonari sarcoidotici e sarcoidosimili, Minerva Pneumol 2:65, 1963.
8. Villar, T. G. and Avila, R.: Diseases of the Lung Due to Inhaled Particles. Similarities and differences in relation to sarcoidosis, In *Proc VI International Conf on Sarcoidosis*. University of Tokyo Press, 1974, p. 136.
9. James, D. G. and O. P. Sharma: Inflammation Due to Sarcoidosis, In *Infective Inflammation*. Hans Huber, Stuttgart, 1968. p. 361.
10. Villar, T. G. and Avila, R.: Sarcoidosis as Seen in Lisbon, Pneumologia 6:1, 1975.
11. Khan, A. and Khan, F. A.: Hypernephroma: A Rare Cause of Bilateral Adenopathy and an Example of Tissue Diagnosis in Suspected Cases of Sarcoidosis, Chest 66:722, 1974.
12. Scadding, J. G.: In *Sarcoidosis*. Eyre & Spottiswoode, London 1967.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Epidemiology

YUTAKA HOSODA

The Epidemiologic Studies of Sarcoidosis in the Past and Future

The research history of sarcoidosis was divided by Siltzbach (1) into four periods, though he gave no particular names to each period. They may be called the single organ involvement period, the multi-organ involvement period, the epidemiologic period, and the immunologic period. As mentioned by him, the epidemiologic period started in 1940s when mass x-ray surveys were introduced into examinations. Through the recent seven international conferences on sarcoidosis, the epidemiologic patterns of occurrence of the disease have gradually been demonstrated.

MacMahon et al pointed out (2) that the main areas in epidemiology are the study of the distribution of disease (descriptive epidemiology) and the search for the determinants of the noted distribution (analytic epidemiology). The epidemiology of sarcoidosis seems to have been concerned mainly with the descriptive area and has begun to take a forward step to the analytic area. This article is a brief review of the patterns of the disease occurrence based on the world literature (3–8) and includes some comments.

Patterns of Occurrence of Sarcoidosis

According to the epidemiologic principles, the patterns will be described very briefly below from 3 aspects; who is attacked and when and where the disease is frequent.

The patients are frequently in their twenties and thirties. The sex difference is not great although both male and female predominance has been reported. Racial susceptibility is notable, blacks being more frequently affected than whites. The parental age and birth order have not been mentioned in the literature, probably because the results were not significant. In the majority of papers, professional persons are reported to contract the disease more frequently than the nonprofessionals. As a reason, we can think that the former will have more chance to see physicians than the latter. The familial aggregation is evident in most papers. Individual predisposition will be discussed below.

The geographical distribution (9, 10) of the disease in Europe and Asia generally shows a north-to-south decline, while it shows the southern predominance in the United States. Except for the United States, the geographic distribution is parallel to the climate, namely the disease incidence is higher in cold areas than in warm areas. This tendency is clearly recognized in the countries covering a long range of latitude with a short range of longitude like Italy and Japan. Urban-rural differences have not been clearly estab-

From the JNR Central Health Institute, Shibuya, Tokyo 151, Japan.

lished. Local outbreaks of sarcoidosis have only been reported in Sweden (11) and Japan (12). The effect of changes in patients' residences, if confirmed, could prove an important key to the epidemiologic problem. James pointed out that young Irish women going to London often contract sarcoidosis-induced erythema nodosum. Hokkaido in Japan has a higher incidence of the disease than any other Japanese district. The race of Hokkaido is no different from that in Japan proper, because nearly the entire population emigrated from Japan proper during the last 100 years. Nevertheless, the Hokkaido population has a higher rate of sarcoidosis than do descendants of the population that remained in Japan proper. This difference suggests that influential causative factors may be present in greater concentration in the Hokkaido region than elsewhere in Japan.

It is agreed that the disease has been found increasingly during the recent 100 years since the Hutchinson's first case. During the period, many environmental factors are thought to have changed. Tuberculosis is often regarded as a secularly changing factor since it has been decreasing so markedly. It is well known that in the countries in which tuberculosis prevalence has been decreasing, sarcoidosis appears increasingly. In Asian and African countries in which tuberculosis prevalence is still high, only isolated case reports have been presented. One may ask whether such a low frequency of sarcoidosis mainly is caused by a lack of awareness of the disease by local physicians. This may be true in part, but not entirely. In 1940 when tuberculosis prevalence was still high in Japan, a large group of workers was given tuberculin tests and x-rayed by Chiba and his colleagues (10) several times a year. Through extensive examinations, they found no bilateral hilar lymphadenopathy (BHL) cases showing negative tuberculin responses. The few BHL cases detected were all tuberculin positive. Recently, Izumi and his colleagues (13) read some 47,000 mass x-ray films taken of North Korean university students and bank workers. No BHL was found attributable to sarcoidosis. Their data indicate that even in the cold climate of North Korea, the prevalence of sarcoidosis is at least below 1.0 per 47,000 young generation. From these results mentioned above, it will be reasonable to think that sarcoidosis will not be prevalent before tuberculosis, an environmental factor, is lowered to certain levels. From published statistics, sarcoidosis tends to appear frequently in countries in which tuberculosis mortality has fallen below 20 per 100,000.

Seasonal variation in the occurrence of sarcoidosis has been reported in a few articles (10). A series of our studies disclosed that the rate of onset was highest in early summer. If one speculates that the causative factors may have worked several months earlier than the peak onset period, the winter or early spring may be the periods when the disease actually begins in most cases. This assumption may correlate with the frequent occurrence of the disease in the cold climatic area. Time and place are so closely related that the two cannot be discussed separately. As an inclusive study, time-space clustering is a method to be employed. Our time-space study (10) gave negative results. However, the negative data may imply that if sarcoidosis is a transmissible disorder, its transmissibility is not so strong as to produce a positive result in time-space clustering.

Cohort and case control studies are essential when carrying out an epidemiologic study. There have been no cohort studies published because difficulty arises in selecting subjects and following them. Our case control study yielded no positive results with nearly 100 items examined in the matched pairs.

Detection and Collection of Latent Sarcoidosis

Cases of sarcoidosis usually are collected by notification (compulsory or voluntary), enquete surveys in a district, or intrahospital surveys. In measuring the frequency of a disease, the use of uniform measures is always required. As parameters, incidence and prevalence in a general or selected population are usually employed. However, such frequencies vary with the methods of case detection. One must know the collection method before comparing one result with another. In sarcoidosis detection, two major sources are available: investigation of symptoms or coincidental findings and mass x-ray surveys. Symptomatic cases may have acute onset characterized by fever, arthralgia, malaise, erythema nodosum, or insidious onset characterized by shortness of breath, heart disturbances, and chronic skin eruptions. If the patients are insensitive to their symptoms or cannot afford medical care, the number to be detected will be smaller than the true incidence. The majority of the cases will remain undetected. Once when the method of case collection is established, the overall frequencies of the disease largely depend on what percentage of the population has been subjected to mass chest x-rays. To illustrate the problem, let us examine the results obtained from two groups in which the mass x-ray attendance rate was different. The first figures (14) come from the results of notification of the disease in a large group comprising nearly half a million workers, 98% of whom have been mass x-rayed annually. The second group of figures comes from the results of enquete surveys throughout Japan in which 40% of the population has been mass x-rayed every year. In the first group, the average annual incidence rate was 1.5 per 100,000 during the period, 1961 through 1970, while in the second group, the incidence was 0.2 per 100,000 during the period 1963 through 1972. The lower rate (or less than one-seventh that of the more closely monitored first group) was produced by a combination of a low attendance rate with mass x-ray surveys, voluntary response to enquete, and the use of the general population that includes infants. In the closely monitored first group, among the 66 cases discovered, about 85% were detected by annual mass x-ray surveys, 10% by symptoms and 5% were incidental findings. The total number of cases was roughly 10 times that of the symptomatic cases. In the second group, among about 2,000 cases collected, 50% were detected by mass x-rays, 40% by symptoms and 10% by coincidental findings. With regard to BHL, a sign of recent onset, almost all cases in the first group exhibited BHL, while in the second group, 90% of the mass x-ray cases, 85% of the symptom cases, and 90% of those with incidental findings had BHL. These figures indicate that most cases were fresh regardless of means of discovery. If the result in the almost universally x-rayed first group could be applied to other groups only partly mass x-rayed, the number of the cases detectable would be estimated at 10 times that of the symptomatic cases. The hypothetical figure would make the estimated number of the cases in the second group as many as 8,000. Generally speaking, case-finding in combination with complete notification yield the richest and soundest epidemiologic data.

Susceptibility According to Sex

Data concerning the sex difference in the cases with sarcoidosis have been diverse. This divergence seems mainly to be caused by the methods of detection, as sex linkage has not been reported. Where mass x-ray surveys are attended predominantly by males, the frequency of male patients would be necessarily higher than that of females. Table I shows the overall incidence of the disease in the above-mentioned second group. In the ages below 29, the male incidence surpasses that of the female, while in the ages older than 30 the female rate exceeds that of the male. The incidence in both sexes are shown in Table II and III according to the manner of discovery—mass x-ray cases and symptomatic cases. In the ages below 29, the male incidence is higher than that of the female in the mass x-ray group, while the male incidence is nearly the same as the female in the symptom-detected cases. In young age groups up to early 20s, attendance rates in mass x-rays are nearly the same in both sexes. The higher incidence of males in these ages may reflect a real difference. On the other hand, in the ages over 40, the female incidence is higher than that of the male, regardless of the means of discovery, especially in the symptom-detected cases. From the above-mentioned results in combination , it can be said that in the ages below 29 males may be more susceptible to sarcoidosis than females, while in the ages over 40 females may be more susceptible to it than males. The turning point may come at their 30s. Further investigations should be made before interpreting the causes of this sex difference.

Immunoepidemiologic Indicators

It is generally accepted that sarcoidosis patients show T and B cell abnormalities, but it is difficult to relate the abnormalities to the etiology of the

TABLE I

Age-Specific Annual Incidence of all Cases with Sarcoidosis (1963–1972)

Age (yrs)	Number			Rate*			
	Total	M	F	Total	M		F
Totals	2,079	991	1,088	0.20	0.19		0.20
9	29	15	14	0.02	0.02	=	0.02
10–19	436	236	200	0.25	0.27	>	0.24
20–29	899	509	390	0.45	0.51	>	0.39
30–39	331	144	187	0.20	0.17	<	0.22
40–49	190	36	154	0.14	0.06	<	0.22
50–59	133	32	101	0.14	0.08	<	0.20
60–69	52	15	37	0.08	0.05	<	0.10
70	9	4	5	0.02	0.02	=	0.02

* Rate per 100,000 based on the 1970 population census in Japan.

TABLE II

Age-Specific Annual Incidence of Cases Detected by Mass X-Rays

Age (yrs)	Number			Rate*			
	Total	M	F	Total	M		F
Totals	1,033	583	450	0.10	0.11		0.08
-9	23	12	11	0.01	0.01	=	0.01
10–19	316	182	134	0.18	0.21	>	0.16
20–29	464	286	178	0.23	0.29	>	0.18
30–39	145	74	71	0.09	0.09	=	0.09
40–49	56	18	38	0.04	0.03	<	0.05
50–59	20	7	13	0.02	0.02	<	0.03
60–69	7	3	4	0.01	0.01	=	0.01
70–	2	1	1	0.00	0.01	>	0.00

* Rate per 100,000 based on the 1970 population census in Japan.

TABLE III

Age-Specific Annual Incidence of Cases Detected by Symptoms

Age (yrs)	Number			Rate*			
	Total	M	F	Total	M		F
Totals	799	289	510	0.08	0.06		0.10
-9	3	1	2	0.00	0.00	=	0.00
10–19	81	35	46	0.05	0.04	<	0.05
20–29	310	156	154	0.16	0.16	>	0.15
30–39	150	51	99	0.09	0.06	<	0.12
40–49	118	15	103	0.09	0.02	<	0.15
50–59	98	18	80	0.11	0.04	<	0.16
60–69	33	11	22	0.05	0.03	<	0.06
70–	4	2	4	0.01	0.01	<	0.02

* Rate per 100,000 based on the 1970 population census in Japan.

disease because of the lack of data regarding lymphocyte populations prior to the onset of the disease. As for HLA genotypes (15) no significant correlation could be established in several papers between HLA groupings and disease occurrence rate.

The deficit in tuberculin sensitivity in patients with sarcoidosis has been recognized since early 1960. Israel (5) has stated that the impaired ability to develop and maintain tuberculin sensitivity observed in the patients recovered from sarcoidosis was a result of a defect which antedated the development of the disease. On the other hand, our study has revealed that the status of tuberculin sensitivity prior to the onset of sarcoidosis did not correlate with the occurrence of sarcoidosis. In fact, the observed distribution of the patients' tuberculin sensitivity prior to disease onset was nearly the same as the expected distribution tuberculin sensitivity when calculated from the population from which the patients were drawn.

Recently, several papers have disclosed raised antibody levels to Epstein-Barr virus (18, 19) in sarcoidosis patients. In this regard, two hypotheses have been proposed. Raised antibody levels might precede the development of sarcoidosis or be merely a consequence of the abnormal immunologic status associated with it. Though no conclusion has yet been drawn, evidence of such acute infection may be difficult to use in support of any etiologic hypothesis, unless the sera of patients had been collected for other purposes. Suitable immunoepidemiologic markers for predicting susceptibility will be those which predate the onset and persist after the disease appears preferably remaining unchanged. Markers have been widely available both in the general or selected populations in which sarcoidosis more commonly may occur. Very recently, we have made an investigation of Hepatitis B antigen in the sera of the sarcoidosis patients (20). The rate of positive results was significantly higher in the patients (10%) than among healthy controls (3%), though the positive anti-Hepatitis B antigen rates were similar in both groups (about 20%). This suggests a prior immunological abnormality to sarcoidosis in the patients. It will take more time before deciding whether Hepatitis B antigen is available as an immunoepidemiologic marker. It is hoped, however, a search for such immunoepidemiologic markers will be conducted. This kind of study may provide us with etiologic clues.

References

1. Siltzbach, L. E.: Sarcoidosis—A Century of Search, Cincinnati J Med 51:187, 1970.
2. MacMahon, B., Pugh, T. F., Ipsen, J.: Epidemiologic Methods, Little, Brown and Company, Boston and Toronto 1960.
3. International Conference on Sarcoidosis, Washington, D. C. June 1–3, 1960: Amer J Resp Dis 84, 5, Part II, 1–183.
4. Proceedings of the Third International Conference on Sarcoidosis, Stockholm, September 11–14, 1963: Acta Med Scand Suppl 425, 1964.
5. La Sarcoidose, Rapports de la IV^e Conference Internationale, Edited by Turiaf, J., Chabot, J., James, D. G., and Zatouroff, M. Masson & Cie, Paris, 1967.
6. Fifth International Conference on Sarcoidosis, Edited by Levinsky L. and Macholda, F. Universita Karlova, Praha, 1971.
7. Proceedings of the VI International Conference, Edited by Iwai, K. and Hosoda, Y. University of Tokyo Press, Tokyo, 1974.
8. Seventh International Conference on Sarcoidosis and Other Granulomatous Disorders, Edited by Siltzbach L. E. Ann N Y Acad Sci 278, 751, 1976.
9. Hosoda, Y., Hiraga, Y., Odaka, M., Yanagawa, Y., Ito, Y., Shigematsu, I., and Chiba, Y.: A Cooperative Study of Sarcoidosis in Asia and Africa: Analytic Epidemiology, Ann N Y Acad Sci 278, 355, 1976.
10. Seartwell, P. E.: Racial Differences in Sarcoidosis, Ann N Y Acad Sci 278, 368, 1976.
11. Wiman L. G.: Familial Occurrence of Sarcoidosis. Proceedings of VI International Conference on Sarcoidosis, Edited by Iwai, K. and Hosoda, Y. 22, University of Tokyo Press, Tokyo, 1974.
12. Hiraga, Y., Hosoda, Y., and Zenda, I.: A Local Outbreak of Sarcoidosis in Northern Japan, The 2nd European Symposium on Sarcoidosis, November 3–5, 1976, E. Berlin.
13. Report on Epidemiological Studies of Sarcoidosis in South-East Asian Region, Edited by Chest Disease Research Institute Kyoto University, 1975.
14. Hiraga, Y., Hosoda, Y., Odaka, M., Takeuchi, K., Takahara, T., Kondo, K., Kurihara, T., Osada, H., Miura, S., Tameshige, T., Kanatomi, M., Senda, I., Ohtake, H., and Chiba, Y.: Epidemiology of Sarcoidosis in a Japanese Working Group—A ten-year study, Proceedings of VI International Conference on Sarcoidosis. Edited by Iwai, K. and Hosoda, Y. 303, University of Tokyo Press, Tokyo, 1974.
15. Hedfors, E. and Moller, E.: HL-A Antigens in Sarcoidosis. Tissue Antigens 3, 95, 1973, Munksgaad, Copenhagen.

16. Israel, H. L. and Sones, M.: The Tuberculin Reaction in Patients Recovered from Sarcoidosis, La Sarcoidose, Rapports de la IV^e International Conference on Sarcoidosis. Edited by Turiaf, J. Chabot, J., James, D. G., and Zatouroff, M. Masson & Cie, Paris, 1967.
17. Hosoda, Y., Odaka, M., Hiraga, Y., Chiba, Y., Oka, H.: Tuberculin Sensitivity Prior to the Onset of Sarcoidosis, Fifth International Conference on Sarcoidosis. Edited by Levinsky, L. and Macholda, F. University Karlova, Praha 1971.
18. Byrne, E. B., Evans, A. S., Fouts, D. W., and Israel, H. L.: Serological Hyperreactivity to Epstein-Barr Virus and other Viral Antigens in Sarcoidosis, Proceedings of VI International Conference on Sarcoidosis, Edited by Iwai, K. and Hosoda, Y. University of Tokyo Press, Tokyo, 1974.
19. Hirshaut, Y., Glade, P., and Viera, L. O.: Sarcoidosis, Another Disease Associated with Serologic Evidence for Herpes-like Virus Infection. N Engl J Med 283, 502, 1970.
20. Hiraga, Y., Hosoda, Y., and Odaka, M.: HBs Antigens in Patients with Sarcoidosis, The 16th General Assembly of the Japan Society of Chest Diseases 14, 1976.

The Mount Sinai Journal of Medicine
Vol. 44, No. 6, November–December, 1977
Printed in U.S.A.

Fiberoptic Bronchoscopy in the Diagnosis of Sarcoidosis

ALVIN S. TEIRSTEIN, MING T. CHUANG, A. ROGELIO CHOY, and ALBERT MILLER

The diagnosis of sarcoidosis depends upon the correlation of a compatible clinical picture with the demonstration of noncaseating epithelioid granulomas in organ biopsy specimens or a positive Kveim-Siltzbach test.

The impressive frequency with which fiberoptic bronchoscopic biopsies have recently been yielding specimens of bronchial wall and lung parenchyma containing noncaseating epithelioid cell granulomas, prompts us to assess what place this procedure should now occupy in our diagnostic investigations of sarcoidosis and how important an addition this technique is likely to be (1–3). It is already clear that fiberoptic bronchoscopy is, to a large degree, replacing scalene fat pad and mediastinal lymph node biopsy and has virtually eliminated open lung biopsy procedures for obtaining tissue-confirming support of the diagnosis. Even in centers where efficient Kveim-Siltzbach intracutaneous test suspensions are employed as an initial screening procedure in suspects, fiberoptic bronchoscopic biopsy, as this study shows, has proved a very useful adjunctive technique among patients with intrathoracic sarcoidosis already in its later stages who may be unresponsive to the Kveim-Siltzbach test suspensions. The addition of the fiberoptic bronchoscopic biopsy technique has also affected the sequence in which diagnostic investigations are carried out in sarcoidosis.

Materials and Methods

The Olympus flexible bronchofiberscope type BF-5B2 was used in each procedure. Bronchoscopy was carried out after premedication and under local anesthesia with the patient fully awake as previously described. (4).

Sixty-two patients for whom a diagnosis of sarcoidosis could eventually be established with tissue confirmation underwent fiberoptic bronchoscopy. The study group consisted predominantly of sarcoidosis suspects with intrathoracic lesions who had already undergone partial screening including the usual clinical and biochemical investigations before being selected for the bronchoscopic procedure. In 49 of the 62 patients, these investigations also included a Kveim-Siltzbach test either before, at the same time, or shortly after, the bronchoscopic procedure.

Kveim-Siltzbach tests were performed with validated Chase-Siltzbach type 1 suspensions of sarcoid spleens J and B which are constantly monitored for specificity and sensitivity (5). The patients had been referred for bronchoscopy by the Sarcoidosis Clinic and Medical Service of The Mount Sinai Medical Center. In a few patients, sarcoidosis was not among the favored

From the Department of Medicine, Pulmonary Division, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

preoperative diagnoses and the finding of granulomas was unexpected. Four patients with known sarcoidosis required the procedure because of significant hemoptysis.

Eight patients belonged to radiographic stage I sarcoidosis (bilateral mediastinal lymph node enlargement with normal lung fields), 20, to stage II sarcoidosis (bilateral mediastinal lymph node enlargement and pulmonary infiltrations), 34, to stage III sarcoidosis (pulmonary infiltrations with no mediastinal lymph node enlargement).

Not all of the patients suspected of having sarcoidosis who underwent bronchoscopic investigation have been included in this study. For example, four asymptomatic patients with bilateral hilar lymphadenopathy who had negative Kveim-Siltzbach tests and negative bronchoscopic biopsies refused further diagnostic investigations and were omitted.

Results

Table I shows that in 48 of the 62 patients (77%), bronchoscopic biopsy specimens revealed noncaseating epithelioid granulomas consistent with those found in sarcoidosis. In the remaining 14 patients (23%) no such granulomas could be detected. Among eight patients in stage I, the tissue biopsy specimens were positive in six (75%); among 20 in stage II, specimens were positive in 17 (85%); and of 34 patients in stage III, 25 (74%) yielded positive biopsies.

Among the 14 patients whose bronchoscopic biopsy specimens failed to reveal granulomas, 6 had chronic pulmonary sarcoidosis of several years duration with unchanging chest radiographs demonstrating extensive fibrosis and bullous transformation which had been present for more than two years. For these 14 patients with negative bronchoscopic biopsies, tissue support for the diagnosis of sarcoidosis was obtained from biopsies of other organs in seven instances and positive Kveim-Siltzbach tests in seven others.

In Table II, results of bronchoscopic biopsies and of the Kveim-Siltzbach test have been compared among 49 patients undergoing both procedures. Twenty-five (51%), or just over half of these 49 patients, did not respond to the skin test, a failure which was the main indication for proceeding with the bronchoscopic biopsy investigation. Granulomas were found in 19 of the 25 or 78%. Since 23 of these 25 patients had radiographic stage II and stage III pulmonary sarcoidosis, the positive bronchoscopic biopsies represented a substantial enrichment of diagnostic results at the stages of the disorder

TABLE I

Results of Flexible Bronchoscopic Biopsy in 62 Patients with Sarcoidosis

X-ray stage	Total number	Positive biopsy	Negative biopsy	% Positive
Stage I	8	6	2	75%
Stage II	20	17	3	85%
Stage III	34	25	9	74%
Total	62	48	14	77%

TABLE II

Comparison of Flexible Bronchoscopic Biopsy and Kveim-Siltzbach Test in 49 Patients with Tissue Confirmed Sarcoidosis

X-Ray Stage	Number	Bronch. Bx + Kveim +	Bronch. Bx + Kveim −	Bronch. Bx − Kveim +	Bronch. Bx. − Kveim −
Stage I	7	4	1	1	1
Stage II	16	8	6	1	1
Stage III	26	6	12	4	4
Total	49	18	19	6	6

when specific skin reactivity tends to fall off. Thus, as Table II also shows, without the addition of the bronchoscopic biopsy investigation, only the 19 of 42 (45%) stage II and stage III patients, who had responded to the skin test, would have possessed the required tissue support for the diagnosis. In sum, a positive result was achieved by either a bronchoscopic biopsy or the Kveim-Siltzbach skin test or by both, in 43 or 88% of the 49 patients and for the entire study group of 62 patients, in 55 or 89%. The remaining seven patients required biopsy confirmation from other sites, six from scalene fat pad biopsies, and one from an open lung biopsy.

Three patients suffered small pneumothoraces which soon absorbed spontaneously. Two had hemoptyses each totaling about 200 cc. No patients experienced any other untoward side-effect from the premedication, local anesthesia, or from the procedure itself.

Discussion

Sarcoidosis is a systemic disease offering many tissue sites for biopsy diagnosis. Skin, lymph node, lacrimal, palatal, and muscle biopsies have all been reported to yield a significant percentage of positive biopsies. Bronchial biopsy with the rigid bronchoscope in sarcoidosis has been employed to good effect by several investigators (6–9). With the introduction of the flexible forceps by Fennessy (10), and the fiberoptic bronchoscope by Ikeda (11), diagnostically confirmatory bronchial and lung biopsies have been reported in as high as 91% of patients with sarcoidosis (1).

At The Mount Sinai Medical Center, the diagnosis of sarcoidosis is established in the overwhelming majority of patients by the intracutaneous Kveim-Siltzbach test. With this highly specific test, Siltzbach has reported a 92% positive diagnosis in 311 patients with sarcoidosis (12). It must be emphasized that the 62 patients who constitute the group who underwent bronchoscopy were specially selected for the procedure. The study population includes an unduly large representation of patients who had a negative Kveim-Siltzbach test (51%) as well as those too ill to wait the four to six weeks required for maturation of the Kveim-Siltzbach test.

Patients exhibiting diffuse pulmonary infiltrations with no discernible mediastinal lymphadenopathy (stage III), often present a diagnostic challenge since similar radiographic patterns are encountered in a host of interstitial pulmonary diseases. It is in this group that Siltzbach has reported the

Kveim test to be of lesser help (13). In 1963, Friedman, Blaugrund and Siltzbach (9) underscored the value of bronchoscopic biopsy specimens obtained with the rigid bronchoscope in patients with chronic sarcoidosis particularly among those with negative Kveim tests. Turiaf and Battesti, (15) routinely employing bronchial wall biopsies via a rigid bronchoscope, found granulomas in specimens of 142 (43%) of 329 patients, more than half of whom were in stages II or III.

The present study group undergoing fiberoptic bronchoscopy was heavily weighted with patients in the more advanced stages of sarcoidosis. Thus, 54 of the 62 (87%) had stage II and stage III disease and only eight (13%) had stage I. This stage distribution stands in marked contrast to the grouping of the entire patient load previously reported. Overall in that series 43% of the patients were in stage I, 35% in stage II and 14% in stage III (8% had normal chest radiograms) (14). In the current study, many of the patients as staged, underwent diagnostic bronchoscopy primarily because the Kveim-Siltzbach test was negative. It is not surprising that positive intracutaneous tests were present in only 49%. Indeed, many of the positive Kveim tests followed the bronchoscopic diagnosis and were performed for confirmation of the diagnosis.

The pathologist must exercise great care in interpreting the histologic alterations found in the small 2 mm biopsy specimens obtained by the flexible forceps. The finding of noncaseating epithelioid granulomas in any biopsy specimen is a nonspecific one. In two patients not included in this series bronchoscopic biopsies showed noncaseating epithelioid granulomas, thought to be consistent with sarcoidosis. In both, the Kveim-Siltzbach test was negative and cultures obtained at bronchoscopy eventually grew out tubercle bacilli. In a third patient, a bronchoscopic biopsy specimen was reported to show caseating epithelioid granulomas, consistent with tuberculosis. However, there was no improvement in the patient's clinical status with antituberculous medication and a Kveim-Siltzbach test was subsequently found to be positive. Open-lung biopsy confirmed the diagnosis of sarcoidosis. Thus, the small fragment of tissue obtained at bronchoscopy may be inadequate for definitive pathologic diagnosis. This experience has reemphasized the importance of performing confirmatory Kveim-Siltzbach tests whenever possible and, if necessary, supplementary biopsies from other organ sites.

Summary

Fiberoptic bronchoscopic biopsies revealed noncaseating epithelioid granulomas consistent with the diagnosis of sarcoidosis in 48 of 62 patients (77%).

By selection, the study group contained a higher proportion of patients with advanced pulmonary sarcoidosis than is found in the usual roster of patients with this disease. Only eight had stage I lesions while 54 of the 62 patients already had stage II or III sarcoidosis when they presented for bronchoscopy.

Since reactivity to Kveim-Siltzbach suspensions may be lost in patients in the later stages of sarcoidosis, when fiberoptic bronchoscopy biopsy findings are frequently positive, these procedures have become complementary in the diagnosis of sarcoidosis.

In this study, 55 of the 62 patients (89%) had the diagnosis of sarcoidosis established by either a positive bronchoscopic biopsy, a positive Kveim-Siltzbach test, or both.

It is clear that, particularly in centers where reliable Kveim-Siltzbach suspensions are not readily available, fiberoptic bronchoscopic biopsy under local anesthesia should assume a central role for obtaining tissue corroboration of the diagnosis of intrathoracic sarcoidosis promptly and with little hazard.

References

1. Koerner, S. K., Sakowitz, A. J., and Appelman, R. I.: Transbronchial Lung Biopsy for the Diagnosis of Sarcoidosis, N Engl J Med 293:268–270, 1975.
2. Joyner, L. R. and Scheinhorn, D. J.: Transbronchial Forceps Lung Biopsy through the Fiberoptic Bronchoscope, Chest 67:532–535, 1975.
3. Teirstein, A. S., Chuang, M. T., Miller, A., and Siltzbach, L. E.: Flexible Bronchoscope Biopsy of Lung and Bronchial Wall in Intrathoracic Sarcoidosis. VII International Conference on Sarcoidosis and Other Granulomatous Disorders, Ann NY Acad Sci 278:522–527, 1976.
4. Teirstein, A. S., Chuang, M. T., and Miller, A.: Application of the Flexible Bronchoscope, Mount Sinai J Med 42:81–94, 1975.
5. Siltzbach, L. E.: Qualities and Behavior of Satisfactory Kveim Suspensions. VII International Conference on Sarcoidosis and Other Granulomatous Disorders, Ann NY Acad Sci 278:665–669, 1976.
6. Benedict, E. H. and Castelman, B.: Sarcoidosis with Bronchial Involvement, N Engl J Med 224:186–189, 1941.
7. Olsen, H. M.: Boeck's Sarcoid: Report of Case in which Diagnosis Was Made by Bronchoscopic Exam and Biopsy, Ann Otol 53:629–637, 1946.
8. Jacob, E.: Sarcoidosis Lesions Revealed by Bronchoscopy, Acta Clin Belg 4:301–310, 1949.
9. Friedman, O. H., Blaugrund, S. M., and Siltzbach, L. E.: Biopsy of the Bronchial Wall as an Aid in Diagnosis of Sarcoidosis, JAMA 183:120–124, 1963.
10. Fennessy, J. J.: Bronchial Brushing and Transbronchial Forceps Biopsy in the Diagnosis of Pulmonary Lesions, Dis Chest 53:377–389, 1968.
11. Ikeda, S.: Flexible Bronchofiberscope, Ann Otol Rhinol Laryngol 79:916–919, 1970.
12. Siltzbach, L. E.: Current Status of the Nickerson-Kveim Reaction, Am Rev Resp Dis (Suppl) 84:89–93, 1961.
13. Siltzbach, L. E.: The Kveim Test in Sarcoidosis—A Study in 750 Patients, JAMA 178:476–482, 1961.
14. Siltzbach, L. E.: Sarcoidosis: Clinical Features and Management, Med Clin North Am 57:483–502, 1967.
15. Siltzbach, L. E., James, D. G., Neville, E., Turiaf, J., Battesti, J. P., Sharma, O. P., Hosoda, Y., Mikami, R., and Odaka, M.: Course and Prognosis of Sarcoidosis around the World, Am J Med 57:847–852, 1974.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Possible Role for Anticoagulant Treatment in Sarcoidosis

EVA HEDFORS

The treatment of sarcoidosis has so far been unsatisfactory. Although in most cases of the disease the prognosis is favorable, with complete recovery within two years, during which period the patient has no symptoms (1), there is always a risk that patients with long-standing disease will eventually develop progressive pulmonary fibrosis. Corticosteroids, which are often used in these cases or instituted because of the presence of respiratory symptoms, usually lead to an immediate symptomatic relief and a regression of the pulmonary infiltrations. However, in most cases their effects have been found to be only suppressive or temporary, without decisively affecting the long-term outcome of the disease (2, 3).

We have recently observed a 32-year-old woman who had had sarcoidosis since the age of 24 and whose extensive pulmonary infiltrations had not responded satisfactorily to corticosteroids but had completely disappeared when the patient was placed on anticoagulants for an unrelated phlebitis (4).

Although the eventual outcome of sarcoidosis is never predictable and, however rare, complete and permanent recovery may be seen even after eight years of disease activity as in the present case, a beneficial effect of anticoagulant treatment in sarcoidosis must be considered and possible mechanisms will be discussed.

The pathogenetic mechanism of sarcoidosis is still unknown. However, the histopathologic picture with extensive epitheloid cell granuloma formations in the affected organs might indicate that a delayed hypersensitivity mechanism may be implicated (5).

The finding of circulating immune complexes in sera from patients with sarcoidosis of acute onset during the initial phase of the disease might, however, also imply that the granulomas are initiated by a humoral immune mechanism (5). Deposits of immunoglobulins and complement (C3) have also, in addition to fibrinogen, been found in the affected organs (6).

It has earlier been shown that anticoagulants affect delayed hypersensitivity (DH) reactions (7, 8). After intraperitoneal, intravenous or subcutaneous injection of antigen into guinea pigs primed for DH, peritoneal macrophages adhere to each other and to the peritoneal serosal cells. The reaction, which is called macrophage disappearance reaction (MDR), does not occur in normal animals or in animals with pure Arthus hypersensitivity (7). The reaction in DH-primed animals is inhibited by warfain and heparin. In contrast, the effect of cortisone acetate is of slight degree and largely accounted for by the decrease in the number of macrophages initially present in the exudates (8).

From the Department of Thoracic Medicine, Karolinska Hospital, Stockholm, Sweden.

Furthermore, in BCG-primed animals treated with heparin or warfain, the tuberculin skin reaction after 48 hours is smaller than in the controls. Treatment with cortisone produces slightly less inhibition of the reactions, whereas the combined treatment with cortisone and anticoagulants produce the most marked inhibition. The inhibitory effect of anticoagulants on macrophage accumulation seems to be dependent on the presence of antigen (8), whereas cortisone seems to reduce the number of macrophages available (8, 12).

The suggestion that macrophage adherence may be mediated by the activation of the clotting system is further substantiated by the finding that fibrin binds to the surface of guinea pig peritoneal macrophages to a still unidentified receptor, which is distinct from that for cytophilic IgG and C3 (9). Moreover, recent studies have demonstrated that fibrin accumulation is a prominent and consistent feature of delayed hypersensitivity skin reactions in man and is responsible for the characteristic induration (10, 11). Whether the induration is brought about by soluble factors (lymphokines) from activated T lymphocytes has been discussed (9).

Anticoagulants have already been widely used alone or in combination with anti-aggregates (e.g., dipyramidole, acetylsalicylic acid) in the treatment of clinical conditions with immunoinflammatory tissue damage, where the role of thrombosis and fibrin deposition is evident. A beneficial effect of anticoagulants has been reported in kidney and heart allografts (13, 14), proliferative glomerulonephritis (15), systemic lupus erythematosus (16), and thrombotic microangiopathy (17).

So far, anticoagulant therapy seems not to have been used in a purely granulomatous condition. If this is to be done in sarcoidosis, it must be remembered that the prognosis is usually favorable without any treatment. Furthermore, the initial granulomatous reaction probably should be considered as a defense mechanism aimed at limiting the spread of the initiating agent. However, it is equally evident that in certain cases, especially of long duration, the granulomatous reaction may be deleterious to the patient. In such situations anticoagulant treatment might be beneficial.

References

1. Siltzbach, L., Immunological Diseases, ed. Samter, p. 581, 1971.
2. Israel, H., Fouts, D. and Beggs, R., Amer. Rev. Resp. Dis. 107:609, 1973.
3. Hedfors, E., Clin. Immunol. and Immunopathol., 4:96, 1975.
4. Hedfors, E., Acta med. Scand. 1977, in press.
5. Hedfors, E., Sc. J. Resp. Dis. 56:1, 1975.
6. Wanstrup, J. and Elling, P., Acta path. microbiol. scand., 73:37, 1968.
7. Nelson, D. and Boyden, S., Immunology, 6:264, 1963.
8. Nelson, D., Immunology, 9:219, 1965.
9. Colvin, R. and Dvorak, H., J. Exp. Med. 142:1377, 1975.
10. Dvorak, H. and Mihm, M., J. Exp. Med. 135:235, 1972.
11. Colvin, R. and Dvorak, H., J. Immunol., 114:377, 1975.
12. Thompson, J. and van Furth, R., J. Exp. Med. 137:10, 1973.

13. Busch, G. J., Kobayaski, K., Kollenberg, N. K., Birtch, A. G. and Colman, R. W., Am. J. Pathol., 80:1, 1975.
14. Griep, R., Wexler, L., Stimson, E., Dong, E. and Shumway, N., J. Amer. Med. Assoc., 221:147, 1972.
15. Clarkson, A., McDonald, M., Cash, J. and Robson, J., Brit. Med. J., 2:255, 1972.
16. Ponticelli, A., Imbasciatti, E., Brancaccio, D., Tarantino, A. and Rivolta, E., Brit. J. Med. 3:716, 1974.
17. Amir, J. and Krauss, S., Blood, 42:27, 1973.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Serum Inhibitors in Sarcoidosis

D. GERAINT JAMES AND EDMUND NEVILLE

Louis Siltzbach received formal postgraduate training as a chest physician and also as a pathologist. This provided a solid background for his research work on sarcoidosis, and it is not surprising that he developed a special interest in immunologic phenomena early in his career. His prolific contributions on the pathogenesis of a skin test, peculiar to sarcoidosis, are recognized internationally, and sarcoidologists around the world have acclaimed his devotion to this cause by adopting the eponymous nomenclature "Kveim-Siltzbach skin test." This essay honors Louis Siltzbach as an international immunosarcoidologist.

Old theories of serum anticutins and procutins in sarcoidosis have been reevaluated now that new techniques of lymphocyte morphology suggest that serum inhibitors are responsible for depression of cell-mediated immunity in sarcoidosis. Depending on the stimulus received, regulator T cells may suppress or amplify the immune response producing lymphokines, which in turn coat or block T cells. In support of this concept is evidence of increased migration-inhibition factors in sarcoid lymphocytes. When sarcoid serum has been removed then there is a return to normal function of these sarcoid lymphocytes. Macrophages are active secretory cells that release potent enzymes perpetuating inflammation leading to granuloma formation, disturbing the traffic of recirculationg lymphocytes, and adding to the depression of cell-mediated immunity. This depression has been overcome by transfer factor both in vitro and in vivo, by blocking or otherwise overcoming serum inhibitors emanating from suppression T cells. Levamisole may act similarly in overcoming depression of delayed-type hypersensitivity in vitro and in treatment.

Almost seventy years ago, Pickert and Löwenstein (1) reported the effect of serum upon the tuberculin response, observations which led to the terms anticutins and procutins. In 1928, Jadassohn (2) introduced his concept that these serum factors were responsible for the specific anergy of sarcoidosis. Sterling (3) demonstrated tuberculin-neutralizing serum in erythema nodosum, and Rostenberg and Brebis (4) noted that both plasma and red cells had a blocking effect on the response both to tuberculin and trichophytin. They felt that blood from sarcoidosis patients had a superior blocking ability compared with blood from controls. Magnusson (5) was unable to demonstrate a local tuberculin blocking effect with topical sarcoid serum.

New methods of measuring lymphocyte transformation, migration inhibition and direct study of T and B lymphocytes permit a fresh look at serum inhibitors and blocking antibodies in sarcoidosis. It is of academic interest to consider their derivation and the effect of any such factors on T cell function,

From the Royal Northern Hospital, Holloway Road, London NY 6LD.

but the problem has also assumed therapeutic importance since transfer factor and levamisole may act at this site in overcoming T cell blockade.

There is increasing evidence of a regulatory population of lymphocytes which most commonly shows T cell characteristics (6). Depending on the stimulus received these cells may cause either suppression or amplification of the immune response, though suppressor and helper populations are probably quite distinct within the umbrella term "regulator T cells." Suppressor T cells are short-lived, poorly recirculating lymphocytes of recent thymic origin which may act directly on other lymphocytes or their effect may be mediated by macrophages (7). If this action were limited to direct contact of cells it would be inefficient, but T cells produce a variety of soluble factors, including migration-inhibition factor (8), specific T cell suppressor factor (9), and specific macrophage-arming factors (10). It should be emphasized that these serum inhibitors differ in their physical properties from antibodies of the five immunoglobulin classes (11) and are not thought to be released by B lymphocytes. Any or all of these factors could be released by suppressor T cells in sarcoidosis leading to depression of cell-mediated immunity.

The release of lymphocyte migration-inhibition factor (MIF) (12) by lymphocytes of 17 sarcoidosis patients was significantly more than healthy controls, but MIF production was not augmented by Kveim extract. Jones Williams and his colleagues (13) were able to produce an MIF from sarcoid lymphocytes by stimulation with Kveim material. Despite different methods both groups of workers demonstrated increased MIF production in sarcoid lymphocytes, reflecting, perhaps, an increase in suppressor T cell activity.

Depression of delayed-type hypersensitivity in sarcoidosis noted by skin tests may be associated with depression of T lymphocyte populations (14-17) or with normal populations (18-22). Mangi and his colleagues (18) suggested that this discrepancy was due to steroid therapy, but they amended this view when they observed steroid-free sarcoidosis patients with entirely normal in vitro sarcoid lymphocyte function when all sarcoid serum had been removed (19). Daniele and Rowlands (22) went a step further to report a specific antibody to T lymphocytes in sarcoidosis which they identified as of both IgG and IgM type. Further work is required to ascertain whether these antibodies act as blocking factors in conjunction with suppressor T cells to cause depression of cell-mediated immunity. Using a migration inhibition test, Morrison (23) showed a consistent in vitro defect in cellular immunity of patients with active sarcoidosis. By adding transfer factor obtained from the blood of normal patients to the previously defective sarcoid lymphocytes, he observed a much enhanced and almost normal response. In vivo a similar result can be demonstrated with local (24) or systemic (25) transfer of delayed hypersensitivity in patients with sarcoidosis. Horsmanheimo and Virolainen (25) transferred systemic delayed hypersensitivity using tuberculin in six of eight patients with sarcoidosis. The skin tests converted to positive and remained so for nine months in parallel with lymphocyte transformation responses to PPD.

Null cells are more frequent than normal in patients with sarcoidosis (20). There is undoubtedly a complex interrelationship between the featureless

Null cell, the depressed T cell, and the exuberant B cell. Serum blocking factors may coat T cells so that they appear as Null cells, which then fail to produce the necessary lymphokines to recruit more T cells. T cell blockade and anergy means lack of suppressor control, thereby allowing B cell overactivity. More work needs to be done to learn whether thymosin and levamisole will transform Null to T cells to correct the situation and whether therapeutic injections of transfer factor will recruit other T cells to repair the defect in cell-mediated immunity.

Summary

Old theories of serum anticutins and procutins in sarcoidosis have been reevaluated now that new techniques of lymphocyte morphology suggest that serum inhibitors are responsible for depression of cell-mediated immunity in sarcoidosis. Regulator T cells may augment the immune-response-producing lymphokines which in turn block T cells. When sarcoid serum is removed from contact with sarcoid lymphocytes, then these lymphocytes function normally. Macrophages release potent enzymes which perpetuate inflammation and lead to granuloma formation which in turn disturbs the traffic of circulating lymphocytes and accentuates the depression of cell-mediated immunity. This depression has been overcome by transfer factor both in vivo and in vitro while levamisole may act similarly.

References

1. Pickert M., Löwenstein E.: Eine neue Methode zur Prüfung der Tuberkulinimmunität, Dtsch Med Wochenschr 34:2262, 1908.
2. Jadassohn, J.: Remarks on Tuberculin in Dermatology, Brit J Dermatol 41:451, 1929.
3. Sterling, K.: Erythema Nodosum with Tuberculin-Neutralizing serum, Am Rev Tuberc 62:(1) 112, 1950.
4. Rostenberg A. Jr., Brebis G. J.: A study of the Blocking Effect of Plasma and of Lysed Red Blood Cells on Delayed Allergic Reactions, J Invest Dermat 23:3, 1954.
5. Magnusson, B.: The Effect of Sarcoidosis Serum on the Tuberculin Response, Acta Derm Venereol (Stockh) 36: suppl. 35, 1956.
6. Humphrey, J. H.: Some Reflections on Principles and Methods of Immunological Tolerance, Br Med Bull 32:182, 1976.
7. Basten A., Miller JFAP., Johnson P.: T cell Dependent Suppression of an Anti-Hapten Antibody response, Transplant Rev 26:130, 1975.
8. Lowe D. M., Lachmann P. J.: The Fractionation of Antigen-Dependent Macrophage Migration Inhibition and Macrophage Activation Factors from Lymph Draining a Tuberculin Reaction, Scand J Immunol 3:423, 1974.
9. Okumura K., Tada T.: Regulation of Homocytotropic Antibody in the Rat. IX. Further characterization of the antigen specific inhibitory T cell factor in hapten specific homocytotropic antibody response, J Immunol 112:783, 1974.
10. Evans R., Grant C. K., Cox H., Steel K., Alexander P.: Thymus Derived Lymphocytes Produce an Immunologically Specific Macrophage Arming Factor, J Exp Med 136:1318, 1972.
11. Asherson G. L., Zembala M: Suppressor T Cells in Cell-Mediated Immunity, Br Med Bull 32:158, 1976.
12. Topilsky M., Siltzbach L. E., Williams M., Glade P. R.: Lymphocyte Response in Sarcoidosis, Lancet 1:117, 1972.

13. Jones Williams W., Pioli E., Jones D. J., Dighero M.: The Kmif (Kveim Induced Macrophage Migration Inhibition Factor) Test in Sarcoidosis, J Clin Path 25:951, 1972.
14. Kataria Y., Bromberg P., Lo Buglio P., Hurtubise P.: Sarcoid lymphocytes: B and T Cell Quantitation. In Proceedings of the VII International Conference on Sarcoidosis, Ed. Siltzbach LE. Ann NY Acad Sci 278:69, 1976.
15. Fernandes B., Press P., Girard J. P.: Distribution and Function of T and B Lymphocytes in Sarcoidosis, Ibid., 278:80, 1976.
16. Veien NK: Immunological Studies in Sarcoidosis. A comparison of disease activity and various immunological parameters, Ibid., 278:47, 1976.
17. Topilsky M., Shohat B., Spitzer S., Joshua H.: Relation Between T Rosette Forming Cells and Cellular Immunity in Sarcoidosis, Ibid., 278:108, 1976.
18. Mangi R. J., Dwyer J. M., Gee B., Kantor E. S.: The Immunological Competence of Subjects with Sarcoidosis, Clin Exp Immunol 18:505, 1974.
19. Dwyer J. M., Mangi R., Gee B., Kantor F. S.: Comparison of the Anergy of Sarcoidosis with Experimentally Induced Anergy in Guinea Pigs. In Proceedings of the VII International Conference on Sarcoidosis, Ed. Siltzbach LE. Ann NY Acad Sci 278:29, 1976.
20. Kalden J. R., Peter H. H., Lohman E., Diehl V., Leibold W. R., Vallee R.: Estimation of T and K Cell Activity in the Peripheral Blood of Sarcoidosis Patients, Ibid., 278:52, 1976.
21. Tannenbaum H., Schur P. H., Rocklin R., Scheffer A. L.: Immunological Identification of Subpopulations of Mononuclear Cells in Sarcoid Granulomas, Ibid., 278:136, 1976.
22. Daniele R. P., Rowlands D. T.: Antibodies to T cells in Sarcoidosis Ibid., 278:88, 1976.
23. Morrison W. L.: Phytohaemagglutinin and Transfer Factor in the Leucocyte Migration Inhibition Test in Patients with Sarcoidosis, Thorax 31:87, 1976.
24. Lawrence H. S., Zweiman B.: Transfer Factor Deficiency Response-A Mechanism of Anergy in Boeck's Sarcoid, Trans Assoc Amer Phys 81:240, 1968.
25. Horsmanheimo M., Virolainen M.: Transfer of Tuberculin Sensitivity by Transfer Factor in Sarcoidosis, In Proceedings of the VII International Conference on Sarcoidosis. Ed. Siltzbach LE. Ann NY Acad Sci 278:129, 1976.

The Mount Sinai Journal of Medicine
Vol. 44, No. 6, November December, 1977
Printed in U.S.A.

Mediators of Delayed Hypersensitivity Reaction in Sarcoidosis

MAIJA HORSMANHEIMO and H. HUGH FUDENBERG

Introduction

Delayed cutaneous hypersensitivity (DH) reaction follows the specific recognition of an antigen by a thymus-derived lymphocyte (T cell). The T cells subsequently undergo proliferation and differentiation, accompanied by secretion of humoral factors termed "mediators of cellular immunity" (MCI). Some of these mediators act on other cells (leukocytes and macrophages), producing the characteristic morphology and time-course of the DH reaction. They also play a role in inflammation and in resistance to fungal, parasitic, and most viral infections. Several dozen mediators have been described, and some have been partially characterized (1–3).

Various studies indicate that both T and B lymphocytes are capable of producing some mediators, such as migration-inhibition factor (MIF), chemotactic factor for macrophages, leukocyte migration-inhibition factor (LIF), and interferon. If B cells produce the same mediators as T cells, the role of B cells in DH must be reevaluated. On the other hand, it has been shown that some mediators, such as lymphocyte mitogenic factor (LMF) and colony-stimulating factor, are produced only by T cells; and at least 15 different activation processes of macrophages by soluble mediators have been described. Thus, in addition to the effect of mediators from lymphocytes, activated macrophages may contribute, for example, through the release of enzymes to the inflammatory response of DH and to resistance to infections.

Mediators of DH can affect the behavior of macrophages, polymorphonuclear (PMN) leukocytes, lymphocytes, and other cell types in vitro, but how many are actually involved in vivo in DH reactions is not known. We discuss here only those mediators of DH which have been studied in sarcoidosis.

Factors Affecting Macrophages

Macrophage Migration-Inhibition Factor (MIF)

MIF was the first mediator described. It was shown that the random migration of cells from spleen fragments obtained from tuberculous guinea pigs was inhibited when the cells were incubated first in vitro with tuberculin. This system was replaced by a capillary tube test in which migrating cells can be peritoneal exudate cells (PEC) of guinea pigs or human mononuclear leukocytes. Sensitive lymphocytes produce MIF in vitro when exposed to specific antigen (antigen-dependent MIF), and under some circumstances they can release MIF when activated by mitogens or other nonspecific stimu-

Publication Number 143, from the Department of Basic and Clinical Immunology and Microbiology, Medical University of South Carolina, Charleston, S.C. 29401. Research supported in part by USPHS Grants HD-09938 and AI-13484.

lants (antigen-independent MIF). MIF production can be detected 4 to 6 hours after lymphocytes have been activated. Human MIF inhibits the migration of human monocytes and guinea pig macrophages. When human buffy coat cell preparations containing polymorphonuclear granulocytes (in addition to mononuclear cells) are placed in capillary tubes. The so-called "leukocyte migration inhibition factor" (LIF) also inhibits migration of polymorphonuclear granulocytes.

Results concerning the ability of sarcoid lymphocytes to release MIF in the presence of antigens have been contradictory. Rocklin (4) reported that sarcoid lymphocytes did not produce MIF but were capable of transforming into blasts when stimulated by antigen. In studies of some 50 patients with sarcoidosis, using guinea pig macrophages as indicator cells, Rocklin et al (5) found that proliferative responses to mitogens and antigens in anergic patients were normal in about 50% of the cases, while MIF production in response to the same antigens was absent in all. These findings suggest a partial defect in lymphocyte function limited to the mediator-producing population. Fernandez et al (6) reported that in spite of negative skin test to Candida albicans and PPD, a moderate production of antigen-dependent MIF from both separated T cells and B cells could be demonstrated in some patients with sarcoidosis. PHA-induced (antigen-independent) MIF release from both T cells and B cells of 15 sarcoid patients was equal to control values (6). In these studies PPD- and Candida-negative human mononuclear cells were used as indicator cells. Using buffy coat cells as indicator cells, Morison (7) found a decreased inhibition of migration in sarcoidosis compared with controls when PHA was used as a stimulant for MIF (and LIF) release.

Contradictory findings have also been reported with regard to MIF release induced by Kveim antigen (8). Inhibition of migration was observed by Hardt and Wanstrup, Becker et al, Jones Williams et al, and Lenzin et al, and by Zweiman and Israel (9) more commonly in patients with sarcoidosis than in controls. Some Kveim suspensions have been reported to inhibit migration in diseases other than sarcoidosis. Negative results in the migration inhibition test in sarcoidosis with Kveim suspensions have been reported by Topilsky et al (10), Rocklin et al (11), and Hard et al (12). The reason for the disparate results probably relates to the type and form of Kveim material used. It should be noted, however, that in studies based on isotope incorporation in DNA-synthesizing blast cells, no significant responses were caused by Kveim materials (13, 14, 15), except in one study (9) in which at least one Kveim preparation in 14 of 45 sarcoid patients and in 4 of the 30 controls induced transformation of lymphocytes.

Macrophage-Activating Factor

Macrophages obtained from animals made immune by infection appear to be activated when cultured in vitro. This phenomenon is also seen when macrophages or monocyte from normal subjects are exposed to lymphocyte mediators. The changes observed in activated macrophages include increased adherence, increased rates of phagocytosis and pinocytosis, increased ruffled membrane activity, increased mobility, enhanced bacteriostasis and tumoricidal activity, increased membrane adenyl cyclase, increased incorporation of glucosamine into membrane components, increased number of cytoplasmic granules, increased levels of lactic dehydrogenase in cytoplasm, increased oxidation of glucose through the hexose monophosphate shunt pathway, and decreased levels of certain lysosomal enzymes. It is not known whether activation of macrophages is induced by MIF or some related factor. It may be that MIF changes the surface properties of cells so that they become more adherent, seen as inhibition of migration, and later the cells become activated and undergo metabolic changes.

Monocyte activation has been reported in sarcoidosis by Kurti and Mankiewicz (16) in leukocyte cultures, by Rechart and Mustakallio (17), and by Kohout (18) in the skin window technique. Accelerated phagocytic activity and increased nuclear RNA synthesis have also been observed in coverslip-attached monocytes (19). Increased lysozyme levels (20) seen in many patients with sarcoidosis suggest also that macrophages produce lysozymes upon activation. Douglas et al (21) have reported that peripheral blood monocytes of patients with sarcoidosis have increased IgG and C3 receptor sites, further suggesting activation of monocytes in this disease.

Factors Affecting Polymorphonuclear (PMN) Leukocytes

Leukocyte Inhibitory Factor (LIF)

PMN leukocytes are inhibited in their migration by a soluble material (LIF) from antigen-stimulated or mitogen-stimulated lymphocytes. Human LIF is distinguishable from human MIF in terms of indicator cells affected, molecular weight, and biochemical characteristics. When human buffy coat cells are used in the capillary tube migration inhibition test, LIF as well as MIF activities are measured. LIF activity can be assayed using purified PMN leukocytes either in capillary tubes as in the MIF system or in agarose. Preincubation of sensitized lymphocytes with specific antigen for 30 minutes inhibits the migration of PMN leukocytes in agarose (direct LMIA test). The same inhibition effect is also seen when PMN leukocytes are preincubated with supernatants from antigen-stimulated leukocyte cultures (indirect LMIA test).

The ability of sarcoid lymphocytes to release LIF has been studied by Zweiman and Israel (9), using different Kveim materials in the direct LMIA test. They found significant inhibition more often in sarcoid patients than in controls. However, differences were not striking and there was considerable overlapping (9). Hard et al (12), using the Danish Kveim material, observed no migration inhibition in the direct LMIA test in 46 sarcoid patients.

Mediators Affecting Lymphocytes

Leukocyte Mitogenic Factor (LMF)

Sensitized lymphocytes stimulated by specific antigen release mediators into the culture fluid which induce nonsensitive lymphocytes to undergo blast transformation in the presence of antigen. Substances with similar activity have also been found to be produced by lymphocytes during stimulation with nonspecific mitogens.

Fernandez et al (6) have shown that sarcoid T cells, as well as lymphocytes from normal healthy controls, stimulated with PHA are capable of releasing LMF. PPD- and Candida-induced LMF release were low in skin-test negative sarcoidosis patients compared with control subjects who were positive in the skin test to these antigens. Sarcoid lymphocytes are also capable of responding to this mediator (22).

Lymphocyte Transforming Factor (LTF)

The effect of a factor released from sensitive lymphocytes during incubation with specific antigen is dependent on antigen dose when low doses of antigen are used. Its release depends also on the skin test sensitivity of the donors. This factor has been called lymphocyte transforming factor (LTF).

Active LTF could not be detected in the supernatants from PPD-stimulated cultures of lymphocytes from patients with sarcoidosis who were tuberculin negative by skin test in vivo and by the lymphocyte transformation test in vitro, or from patients who were only weakly tuberculin positive (100 TU positive) (23). LTF from tuberculin-sensitive patients with sarcoidosis was less active than that from tuberculin-sensitive healthy controls. Thus, LTF is a second mediator (in addition to MIF) whose release might be decreased in sarcoidosis.

Lymphocytes from tuberculin-negative sarcoid patients were capable of responding to LTF which caused an average 8-fold increase in [^{3}H]thymidine uptake by lymphocytes from patients with sarcoidosis who were tuberculin negative both by skin test and in vitro (23). We also observed an increased response with LTF in cultures from patients with sarcoidosis in whom PPD-induced lymphocyte transformation was observed in spite of a negative skin test to tuberculin (23).

Transfer Factor (TF)

Transfer of DH to tuberculin in humans was first demonstrated by Lawrence (24). Sensitized lymphocytes contain a small-molecular-weight substance called transfer factor (TF) which is released when the cells are disrupted or when they are stimulated with a specific antigen. DH and some other parameters of cellular immunity can be transferred by dialyzable leukocyte extracts (DLE, assumed to contain TF) in healthy subjects, as well as in most patients with immunodeficiency diseases. It has also been shown that TF can transfer the ability to produce MIF, and can increase T cell-mediated cytotoxicity and levels of active T cells.

Attempts to transfer systemic delayed hypersensitivity to tuberculin into patients with sarcoidosis using whole leukocytes have not been successful (25). Lawrence and Zweiman (26), using DLE from tuberculin-positive subjects observed acquisition of systemic tuberculin sensitivity in only two of seven sarcoid patients, whereas five of seven acquired local sensitivity. We have demonstrated the acquisition of tuberculin skin test sensitivity by six of eight sarcoid patients after a single injection of DLE from tuberculin-positive healthy subjects (27), using a dosage equivalent to 0.9×10^8 cells as opposed to 0.4×10^8 used by Lawrence and Zweiman (26). We also found that the transferred tuberculin sensitivity was demonstrable by in vitro PPD-induced blast transformation in sarcoidosis. DLE did not cause PPD-induced blast transformation when added directly to cultures of lymphocytes from sarcoid patients (27), in contrast to results reported for normal controls (24).

There are a number of mediators at DH which have not been studied in sarcoidosis, including many that accompany the activation of macrophages, macrophage (monocyte) chemotactic factors, chemotactic factors for neutrophils, basophils, and eosinophils, factors that affect antibody production, cytotoxic factors, and growth inhibitory factors, interferon, tissue factor (procoagulant factor activity), colony-stimulating activity, etc.

In Vivo Significance of Mediators

Skin Reactive Factor

When fluids containing mediators are injected intradermally into guinea pigs, a reaction similar to the classic DH reaction is observed, indicating that these substances may be involved in DH in vivo. In the DH reaction in vivo the majority of the cells are hematogenous and not specially sensitized to the antigen in question. Thus nonimmune cells (leukocytes, basophils, and macrophages) are "recruited" to participate in the reaction. This recruitment is probably mediated in vivo by mediators of DH. Since preparations used to elicit this response (skin-reactive factor) contain several mediators, including MIF, chemotactic factors, LT and mitogenic factors, it is not clear at present whether one or a combination of these is responsible for the development of the skin reaction.

Gross (28) has reported that one "lymphokine" preparation that contained MIF activity (29) in vitro failed to induce skin reaction in eight sarcoid patients when injected intradermally. The same preparation produced an accelerated but otherwise typical DH skin response in 52 of 56 controls. However, most sarcoid patients responded to this mediator preparation when it was injected together with cortisone. Gross concluded that the defect in sarcoidosis is a block in the expression of DH, probably due to a defect in the ability of macrophages to respond to MIF.

Mediator Activity in Serum

It is interesting that MIF and interferon activity can be detected in the serum of animals undergoing immunologic reactions, indicating that lymphokine production also occurs in vivo and not just in vitro in cultures of lymphocytes.

Spontaneous MIF release by sarcoid lymphocytes cultures without any stimulants has been reported (10, 30), suggesting immunological enhancement in the disease. Loehner et al (31) also reported that the reactivity of normal T cells to PHA and ConA was augmented by a soluble amplifier material from lymphocyte cultures of sarcoid patients, and that there was an inverse correlation between the reactivity and the patient's own response to PHA (31). Thus, although the reactivity of normal T cells was augmented by this material, the patient's own T cells were unresponsive to the amplifying effect. Their B-cells, however, were influenced by this material as manifested by increased production of immunoglobulins (31).

Inhibitory factors in sera of sarcoid patients have been reported by many investigators. Belcher et al (32) reported that sera from 10 to 14 patients with sarcoidosis reduced the in vitro transformation of normal lymphocytes in response to Candida and mumps antigens, and 7 of 14 sera reduced the response to PHA. Mangi et al (33) found that lymphocytes from 13 of 26 sarcoid patients did not respond to in vitro stimulation in their own plasma as well as in pooled plasma from healthy donors. Plasma from 14 of 25 patients with sarcoidosis caused a moderate but significant decrease in PHA response of normal lymphocytes. Daniele and Rowlands have reported antibodies to a proportion of T cells in sarcoidosis (34). Serum from nine of fifteen patients with sarcoidosis inhibited the capacity of normal T cells to form E rosettes, with an average reduction of 33% from control values. IgM and IgG antibodies to T cells were also identified using the indirect immunofluorescence method (34), and four of these sera were also cytotoxic to T cells (34). On the other hand, blocked T-cell reactivity has also been suggested to be due to immune complexes found in sera of patients with sarcoidosis (35, 36).

Clinical Significance of Mediators of DH in Sarcoidosis

Anergy or decreased DH to tuberculin and other bacterial, viral, and fungal antigens is often seen in sarcoidosis. There are several alternatives to explain termination or decrease of DH reactivity in general. Removal of the initiator of the reaction by desensitization with a large quantity of antigen, or by depletion of the total number of responding cells (lymphocytes and/or macrophages), or the number of specifically reactive lymphocytes, and/or their lymphokines could terminate or reduce DH reactions. Unresponsiveness of target cells (leukocytes and/or macrophages) to mediators of DH or the presence of an inhibition mechanism could also impair DH reactions.

When unresponsiveness of DH is produced by large doses of antigen in previously sensitized animals, the loss of DH to the sensitizing antigen and to all antigens to which the animal has been sensitized is transient. Only repeated cycles of sensitization and desensitization can produce long-lasting anergy in animals. Although the granulomatous state in sarcoidosis might be associated with persistent stimulus, it is unlikely that the amount of possible antigen is large enough to induce this immunologic tolerance in sarcoidosis. The fact that the anergy of DH in sarcoidosis has a very long duration and is often irreversible also argues against immunologic tolerance as a possible cause.

It is also unlikely that depletion of the total number of T cells is responsible for impairment of DH in sarcoidosis, since there is no striking decrease in the number of T cells associated with this disease. The total number of T cells has been reported to be decreased (6, 37–41) or normal (31). In addition, recent studies indicate that the responsiveness of sarcoid lymphocytes to the T-cell mitogen PHA is almost normal (6, 22, 31, 39, 42), and ConA responsiveness has been reported to be somewhat reduced (39, 43) or normal (31). The appearance of numerous macrophages, epitheloid cells, and giant cells in granulomas and moncytosis often seen in the peripheral blood of patients with sarcoidosis also speaks against the possibility that depletion of monocytes from peripheral blood or depletion of macrophages is responsible for impairment of DH.

Dissociation of skin reactivity, blastogenesis of lymphocytes, ability of lymphocytes to release mediators of DH, or ability of lymphocytes or macrophages to respond to these mediators has been described in many immunodeficiency diseases (24). It seems clear that functional subgroups exist within the lymphocyte population as well as within the monocyte-macrophage population.

The responsiveness of sarcoid lymphocytes to antigen in vitro in spite of negative skin test responses in vivo (4, 5, 39, 44), the almost normal PHA responsiveness of sarcoid lymphocytes (6, 22, 31, 39, 42), and the finding that sarcoid lymphocytes are capable of responding to LMF (22) and to LTF (23) as well as normal lymphocytes suggest that the primary defect in DH reaction in sarcoidosis might not be in the responding capacity of lymphocytes. On the other hand, sarcoid macrophages are capable of enhancing the blastogenesis of lymphocytes to antigen to the same extent as macrophages from healthy subjects (45). Addition of adherent cells from sarcoid patients to T-cell cultures from the same patients has been reported to restore the responses to antigens and mitogens to the level obtained in unfractionated leukocyte cultures (43). Increased activity of macrophages in sarcoidosis has also been reported in several studies (16–21), suggesting that sarcoid macrophages are also capable of responding to many stimuli.

The decrease in DH in sarcoidosis could also be explained on the basis of a defect in one or another lymphocyte subpopulation(s) producing mediators of DH. This could be due either to a lack or decrease of stimulatory mediators (4, 5, 7, 23, 25–27) or to an increase of the inhibitory mediators (32–34) described in sarcoidosis. Lack of stimulatory mediators of DH could be due to some environmental, genetic, or infectious effect on T-cell subpopulations.Alternatively, an increase in inhibitory mediators could be due to activation of suppressor T cells by antigenic stimulus and/or to chronic stimulation which the host is unable to eliminate due to lack of some lymphocyte mediator(s) or to a defect in the ability of macrophages to handle the causative agent. Chronic stimulation, either antigenic or toxic, could be responsible for cell-mediated immunologic granuloma formation (46). Indeed, the fact that no infectious organism or pathogenic antigen has been found in sarcoidosis suggests that the primary defect may well be in the capacity of some subpopulation(s) of lymphocytes or macrophages to handle a variety of causative agents.

Acknowledgment

We thank Charles L. Smith for skillful editorial assistance with the manuscript. This is publication No 143 from the Department of Basic and Clinical Immunology and Microbiology, Medical University of South Carolina.

References

1. Lawrence, E. S. and Landy, M. (Editors): *Mediators of Cellular Immunity,* Academic Press, New York and London, 1969.
2. David, J. R. and David, R. R.: Cellular Hypersensitivity and Immunity. Inhibition of Macrophage Migration and the Lymphocyte Mediators. In *Progress in Allergy,* Edited by P. Kallos, B. H. Waksman, and A. DeWeck. Karger, Basel 1972, p. 300.
3. David, J. R.: Macrophage Activation by Lymphocyte Mediators, Fed Proc 34:1730, 1975.
4. Rocklin, R. E.: Clinical Applications of in Vitro Lymphocyte Tests, Prog Clin Immunol 2:21, 1974.
5. Rocklin, R. E.: Personal communication, J. Invest Derm 67:475, 1976.
6. Fernandez, B., Press, P., and Girard, J. P. Distribution and Function of T- and B- cell Subpopulations in Sarcoidosis, Ann NY Acad Sci 278:80, 1976.
7. Morison, W.L.: Phytohaemagglutinin and Transfer Factor in the leukocyte Migration Inhibition Test in Patients with Sarcoidosis, Thorax 31:87, 1976.
8. Horsmanheimo, M.: Lymphocyte Transformation in Sarcoidosis, Thesis, Helsinki, 1973.
9. Zweiman, B. and Israel, H. L.: Comparative in vitro reactivities of Leukocytes from Sarcoids and Normals to Differential Kveim Preparations, Ann NY Acad Sci 278:700, 1976.
10. Topilsky, M., Williams, M., Siltzbach, L. E., and Glade, P. R.: Lymphocyte Response in Sarcoidosis, Lancet 1:117, 1972.
11. Rocklin, R. E., Sheffer, A. L., and David, J. R.: Sarcoidosis: A Clinical and in Vitro Immunologic study. In *Proceedings of the Sixth Leukocyte Culture Conference,* Edited by M. R. Schwartz. Academic Press, New York and London, 1972, p. 743.
12. Hardt, F., Veien, N., Bendixen, G., Brodthagen, H., Farber, V., Genner, J., Heckscher, T., Ringsted, J., Freiesleben Sorensen, S., Wanstrup, J., and Wiik, A.: Immunological Studies in Sarcoidosis: A Comparison of in Vivo and in vitro Kveim tests, Ann NY Acad Sci 278:711, 1976.
13. Siltzbach, L. E., Glade, P. R., Hirshaut, Y., Vieira, L.O.B.D., Celikoglu, I. S., and Hirschhorn, K.: In vitro Stimulation of Peripheral Lymphocytes in Sarcoidosis. In *Proceedings of Vth International Conference on Sarcoidosis,* Edited by L. Lewinsky and F. Macholda. State Printing House, Prague, 1971, p. 217.
14. Horsmanheimo, M.: Lymphocyte Transformation and the Kveim Test, Lancet 1:1120, 1973.
15. Izumi, T., Nilsson, B. S., and Ripe, E. In Vitro Lymphocyte Reactivity to Different Kveim Preparations in Patients with Sarcoidosis, Scand J Respir Dis 54:123, 1973.
16. Kurti, V. and Mankiewicz, E.: In Vitro Study of Macrophages from Patients with Sarcoidosis, Can Med Assoc J 107:509, 1972.
17. Rechardt, L., and Mustakallio, K. K.: Macrophage Response to Epidermal Abrasion in Sarcoidosis. Its relation to the Patient's Kveim Reactivity, Acta Pathol Microbiol Scand 65:521, 1965.
18. Kohout, J. Macrophage Reactivity in Skin Window of Sarcoidosis Patients, Ann NY Acad Sci 278:201, 1976.
19. Schmidt, M., Havemann, K., Kessler, G. F., and Malchow, H.: Untersuchungen zum Ribonukleinsaure (RNS)-stoffwechsel von Monocyten in vitro bei Gesunden und Patienten mit Sarcoidose, Z Immunitaetsforsch 139:195, 1970.
20. Pascaul, R., Gee, J.B.L., and Finch, S. C.: Usefulness of Serum Lysozyme Measurement in the Diagnosis and Evaluation of Sarcoidosis, N Engl J Med 289:1074, 1973.
21. Douglas, S. D., Doughaday, C. C., Schmidt, M. E., and Siltzbach, L. E.: Kinetics of Monocyte Receptor Activity for Immunoproteins in Patients with Sarcoidosis, Ann NY Acad Sci 278:190, 1976.
22. Girard, J.-P., Poupon, M.-F., and Press, P.: Culture of Peripheral Blood Lymphocytes from Sarcoidosis; Response to Mitogenic Factor, Int Arch Allergy Appl Immunol 41:604, 1971.
23. Horsmanheimo, M.: Lymphocyte Transforming Factor in Sarcoidosis, Cell Immunol 10:338, 1974.
24. Lawrence, H. S.: Transfer Factor in Cellular Immunity, Harvey Lect 68:239, 1974.

25. Urbach, F., Sones, M., and Israel, H. L.: Passive Transfer of Tuberculin Sensitivity to Patients with Sarcoidosis, N Engl J Med 247:794, 1952.
26. Lawrence, H. S. and Zweiman, B.: Transfer Factor Deficiency Response—a mechanism of Anergy in Boeck's Sarcoid, Trans Assoc Am Physicians 81:240, 1968.
27. Horsmanheimo, M. and Virolainen, M.: Transfer of Tuberculin Sensitivity by Transfer Factor in Sarcoidosis, Clin Immunol Immunopathol 6:231, 1976.
28. Gross, N. J.: The Paradoxical Skin Response in Sarcoidosis. A Hypothesis, Amer Rev Respir Dis. 107:798, 1973.
29. Valdimarsson, H. and Gross, N. J.: Human Skin Responses to Products of Concanavalin A - Activated Lymphocytes, J Immunol 111:485, 1973.
30. Kataria, Y. P., Bromberg, P. A., and LoBuglio, A. F.: Sarcoid Lymphocytes: Spontaneous Transformation and MIF Production, Clin Res 20:807, 1972.
31. Loehnen, C. P., DeRemee, R. A., Tomasi, T. B., and Stobo, J. D.: Regulation of Immunologic Reactivity in Sarcoidosis, Ann NY Acad Sci 278:117, 1976.
32. Belcher, R. W., Carney, J. F., and Nankervis, G. A.: Effect of Sera from Patients with Sarcoidosis on in vitro Lymphocyte Response, Int Arch Allergy Appl Immunol 46:183, 1974.
33. Mangi, R. J., Dwyer, J. M., and Kantor, F. S.: The Effect of Plasma upon Lymphocyte Response in vitro. Demonstration of a Humoral Inhibitor in Patients with Sarcoidosis, Clin Exp Immunol 18:519, 1974.
34. Daniele, R. P. and Rowlands, Jr., D. T.: Antibodies to T Cells in Sarcoidosis, Ann NY Acad Sci 278:88, 1976.
35. Hedfors, E. and Norberg, R.: Evidence for Circulating Immune Complexes in Sarcoidosis, Clin Exp Immunol 16:493, 1974.
36. Verrier Jones, J., Gumming, R. H. and Asplin, C. M.: Evidence for Circulating Immune Complexes in Erythema Nodosum and Early Sarcoidosis, Ann NY Acad Sci 278:212, 1976.
37. Hedfors, E., Holm, G., and Petersson, D.: Lymphocyte Subpopulations in Sarcoidosis, Clin Exp Immunol 17:219, 1974.
38. Veien, N. K., Hardt, F., Bendixen, G., Ringsted, H., Brodthagen, H., Faber, V., Genner, J., Heckscher, T. Svejgaard, A., Freisleben Sorensen, S., Wanstrup, J., and Wiik, A.: Immunological Studies in Sarcoidosis: A Comparison of Disease Activity and Various Immunological Parameters, Ann NY Acad Sci 278:47, 1976.
39. Kalden, J. R., Peter, H. H., Lohmann, E., Schedel, J., Diehl, V., and Vallee, D.: Estimation of T- and K-Cell Activity in the Peripheral Blood of Sarcoidosis Patients, Ann NY Acad Sci 278:52, 1976.
40. Kataria, Y. P., LoBuglio, A. F., Bromberg, P. A., and Hurtubise, P. E.: Sarcoid lymphocytes: B- and T- Cells Quantitation, Ann NY Acad Sci 278:69, 1976.
41. Topilsky, M., Shohat, B., Spitzer, S. and Joshua, H.: Relationship Between T-Rosette-Forming Cells and Cellular Immunity in Sarcoidosis, Ann NY Acad Sci 278:108, 1976.
42. Horsmanheimo, M. and Virolainen, M.: Correlation of Phytohaemagglutinin-Induced Lymphocyte Transformation with Clinical Manifestations of Sarcoidosis, Acta Path Microbiol Scand (B) 82:122, 1974.
43. Hedfors, E.: Activation of Peripheral T Cells of Sarcoidosis Patients and Healthy Controls, Clin Exp Immunol 18:379, 1974.
44. Horsmanheimo, M.: Correlation of Tuberculin-Induced Lymphocyte Transformation with Clinical Manifestations of Sarcoidosis, Cell Immunol 10:329, 1974.
45. Horsmanheimo, M., Virolainen, M.: Enhancement of Tuberculin-Induced Lymphocyte Transformation by Precultivated Macrophages from Patients with Sarcoidosis, Scand J Immunol 3:21, 1974.
46. Warren, K. S.: A Functional Classification of Granulomatous Inflammation, Ann NY Acad Sci 278:7, 1976.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November December, 1977
Printed in U.S.A.

Mononuclear Phagocytes in Sarcoidosis and Granulomatous Diseases

STEVEN D. DOUGLAS AND MANFRED E. SCHMIDT

The immunopathogenesis of granuloma formation involves a complex interplay between lymphoid cells, mononuclear phagocytes, immunoproteins, and presumably lymphokines. Evidence derived from animal experimental models indicates that the emigration of circulating monocytes of bone marrow origin has a significant role in the formation of granulomas. In these model systems a distinction has been made between high and low turnover granulomas. The experimental evidence also suggests that the development of epithelioid cells and multinucleate giant cells occurs via mononuclear phagocytes. Recent studies have demonstrated that the cells present in sarcoid granulomas include histiocytes which resemble lymph node histiocytes (1). The factors which regulate the dynamic emigration, proliferation, and differentiation of lymphoid cells and mononuclear phagocytes are complex and their study in man has been limited.

Since the peripheral blood mononuclear phagocyte reflects a dynamic population of cells which may be migrating to or from various tissue sites, and since these cells are readily obtainable, their investigation is justified. Our studies have attempted to assess certain immunologic aspects of the mononuclear phagocyte in normal individuals, patients with sarcoidosis and other granulomatous diseases. It is our intent in this discussion to consider certain aspects of the structure and function of mononuclear phagocytes which may be of relevance in the immunopathogenesis of sarcoidosis. Various other aspects of the immunology of sarcoidosis have recently been reviewed (2).

Structure, Function and Dynamics of Normal Mononuclear Phagocytes

The blood monocyte appears to have its origin as a stem cell which is present in the medullary space of the bone marrow. These stem cells differentiate into monoblasts, promonocytes and finally, monocytes. Following the last intrabone marrow mitosis, the blood monocyte is released to the peripheral ciculation. The blood monocyte then emigrates to tissues and becomes a tissue macrophage. Tissue macrophages may be free, or present at fixed anatomic sites. Various cells of the mononuclear phagocyte system differ in morphology, functional capabilities and immunologic activities. In general, the cells are characterized morphologically by extensive development or organelles which function in phagocytosis and endocytosis. Mononuclear phagocyte metabolic activity varies with the anatomic location and functional state of the cell. The major metabolic pathways are similar to those in

From the Department of Medicine of the University of Minnesota Medical School, Minneapolis, Minnesota, and the Department of Medicine of the University of Marburg, Marburg, West Germany.

neutrophils and include glycolosis, hexose monophosphate shunt metabolism, and aerobic metabolism.

The "activated" macrophage is a cell which is increased in size and has enhanced phagocytic and microbicidal activity in comparison to the non-activated macrophage. The activated macrophage is characterized by an increase in the size and number of lysosomes, an enlarged Golgi zone and increased ruffling of the plasma membrane. Macrophage activation occurs following in vitro cultivation, exposure to facultative intracellular bacteria, thioglycolate exposure, antigen contact, immune complexes, lipopolysaccharides, polynucleotides, and lymphokine interaction.

The mononuclear phagocyte has plasma membrane binding sites for the Fc portion of immunoglobulin, for the third component of complement ($C3_b$), and for lymphocyte attachment. These receptors may have a direct functional role in phagocytosis and in the immunologic activities of the macrophage. The macrophage has been extensively studied with respect to its role in the afferent phase of the immune response. It has been demonstrated that macrophages bind antigen and that surface bound antigen may be important in antigen presentation to lymphoid cells. The immunobiology of the macrophage has recently been extensively reviewed (3–5).

Peripheral Blood Monocytes in Patients with Sarcoidosis and Other Granulomatous Diseases.

A number of early investigations suggested an increased proportion of circulating monocytes in patients with sarcoidosis. The interpretation of this finding is complicated by the fact that the atypical mononuclear cells observed may be lymphoid in origin and the distinction between these cell types is extremely difficult to detect even by electron microscopy (6).

Studies in our laboratory have been directed toward semiquantitative assessment of receptors for IgG and C3 which are present on the plasma membranes of the peripheral blood monocyte. We have developed assay systems utilizing monocyte enriched populations derived from peripheral blood (7, 8). Monocytes are obtained by layering leukocyte pellets over bovine serum albumin; following centrifugation the monocytes are present as a surface pellicle. The cells are then attached to glass coverslips in Leighton tubes. Various antibody and/or complement coated erythrocyte preparations are added and the slides are evaluated morphologically or by counting the binding of chromium 51-labeled erythrocytes in a gamma counter.

Our studies (9–11) have demonstrated that there is increased activity of monocyte Fc and C3 receptor for cells obtained from patients with active sarcoidosis. We have also demonstrated some increase in activity of Fc receptor for monocytes from patients with Crohn's disease and active tuberculosis (12). In addition, using purified subclasses of IgG_1 and IgG_3 added to the fluid phase as inhibitors of our assay system, we have demonstrated that there is less inhibition of Fc binding for monocytes from sarcoid patients in comparison to normal individuals.

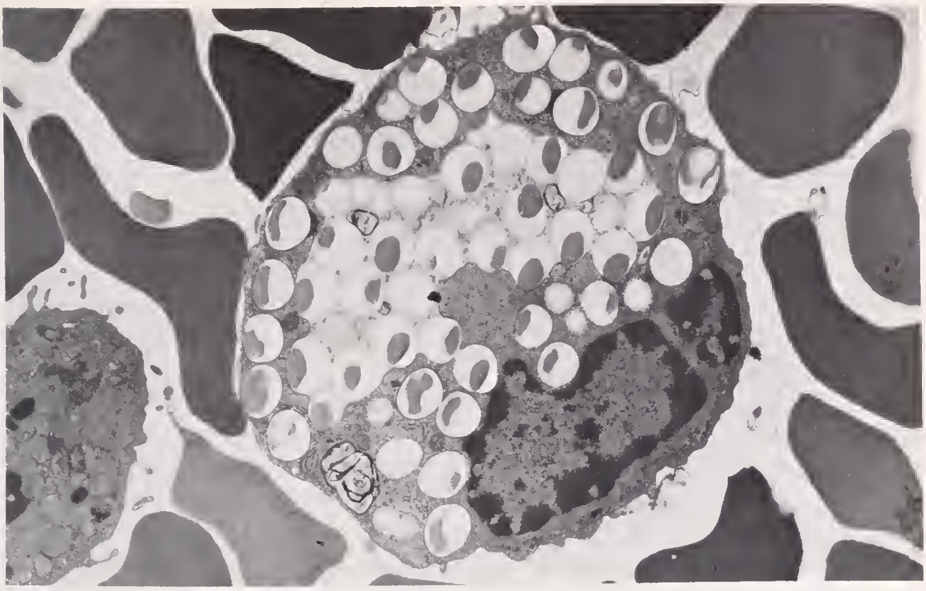

FIG. 1. Monocyte 8 hours following latex phagocytosis. Rosette formation including binding opposite the Golgi zone (where phagocytosis is most active) with EA indicates recovery of IgG receptor activity. Magnification × 8,000.

Our studies of IgG membrane receptor dynamics indicate that following ingestion of inert polystyrene latex particles, Fc receptor activity disappears then recovers in 6–8 hours for normal monocytes (13), whereas activity fully recovers after 2 hours for monocytes (11) from sarcoidosis patients (Fig. 1).

We have recently demonstrated that incubation of normal monocytes with multistranded homoribopolynucleotides results in increased IgG receptor activity (14). In contrast, homoribopolynucleotides had no effect on the Fc receptor activity for monocytes from patients with sarcoidosis and had only a slight effect on monocytes from patients with Crohn's disease. These results suggest that polyribopolynucleotides exert stimulatory effects only on inactive monocytes and do not alter receptor activity for cells which are activated in vivo.

Preliminary studies of cytoplasmic spreading (15) of monocytes from patients with tuberculosis and sarcoidosis indicate that a greater percentage of cells from patients undergo spreading and that the extent of spreading is increased in comparison to cells from control donors. The phenomenon of cytoplasmic spreading of monocyte macrophages is a plasma membrane mediated event, perhaps related to "activation." Cytoplasmic spreading occurs on glass and is enhanced in the presence of certain divalent cations (e.g., manganese), proteolytic enzymes, antigen-antibody complexes, and the immunostimulatory drug, levamisole (16).

Our observations during the past several years of increased monocyte receptor activity for cells from patients with active sarcoidosis, Crohn's disease and tuberculosis probably indicate a type of monocyte "activation."

These findings most likely reflect an alteration in the plasma membrane properties of these cells. Macrophages in chronic inflammatory states in animal models have been demonstrated to contain increased numbers of lysosomes, an increased content of lysosomal enzymes, and increased bactericidal and cytotoxic capacity (17). We interpret the observations of increased IgG and C3 receptors as indicating monocyte activation. Studies of monocytes from patients with tuberculosis have demonstrated increased binding of ^{51}Cr-labeled IgG-coated erythrocytes. LoBuglio et al (18) have also shown increased glycolysis, increased hexose monophosphate shunt activity, and increased ability to kill Staphylococcus aureus for monocytes from patients with active tuberculosis.

Recent evidence suggests that the macrophage populations may be heterogeneous in structure and function. Studies of rabbit alveolar macrophages stimulated in vivo and activated mouse peritoneal exudate cells have demonstrated higher IgG receptor activity than unstimulated controls. Thus, our observations could possibly be consequential to persistance of an etiologic agent. Circulating antigen-antibody complexes have been detected in some patients with early sarcoidosis (2). Immunoglobulin and complement deposits have been detected in lung lesions in some investigations. Mononuclear phagocytes are directly involved in binding, phagocytosis and transport of immune complexes. The relationship between these epiphenomena and granuloma formation remains to be determined.

There have been several investigations of experimental models of granuloma formation. The detailed studies of Dannenberg and his coworkers (19) have characterized the primary dermal BCG lesions in rabbits. These studies have characterized a model for the pathogenesis of tuberculosis. At the sites where bacilli are present there is macrophage accumulation, and the cells develop high levels of lysosomal enzymes. Using radioactive labeling techniques the migration of mononuclear phagocytes into the lesion has been demonstrated. With tuberculin hypersensitivity, there is accelerated mononuclear phagocyte turnover and cell death within the lesions. The levels of beta galactosidase in these cells have been used as a measure of macrophage activation. Activation occurs more rapidly in lesions of reinfection. These studies have delineated a sequence of macrophage emigration, activation and turnover with concomitant local immunity which is operative in tuberculosis.

Many other types of granulomatous inflammation have been investigated including the sequelae of infections with Group A Streptococci and the Schistosome A granuloma. There have been several approaches to the classification of granulomas based on turnover or based on their immunologic or nonimmunologic origin. The studies of Warren and his coworkers (20) of the chronic Schistosoma mansoni granulomas around eggs have demonstrated a gradual alteration in cell-mediated immunity in this model. These events lead to a generalized loss of lymphocyte responsiveness. Although the basis for the sarcoid granuloma remains unknown, perhaps it is related to some form of chronic antigenic stimulation. It appears that the sarcoid granuloma is a complex interaction site between an unknown antigen and mononuclear phagocytes (21). There is active cell turnover, secretory events, cell mitosis, fusion and formation of giant and epithelioid cells. The characteristic Schaumann and asteroid bodies are the end-stage events of this process. The control of macrophage products and their possible interaction with lymphocytes requires further investigation. It is evident that a complex sequence of events determines the trafficking, localization, and functional events of these cells.

In order to determine the role of the mononuclear phagocytes in the pathogenesis of sarcoidosis, further studies of experimental model systems, long term in vitro cultivation of human cells from patients and controls, characterization of secretory products, and monocyte-lymphocyte interaction are essential.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft and the Braum-Melsungen Stiftung, Melsungen, Germany (MES) and by the U. S. Public Health Service Grant AI 12478 from the National Institutes of Health and by the National Leukemia Association, Inc. (SDD).

References

1. Tannenbaum, H., Rocklin, R. E., Schur, P. H., Sheffer, A. L.: Immunological Identification of Subpopulations of Mononuclear Cells in Sarcoid Granulomas, Ann NY Acad Sci 278:136, 1976.
2. James, D. G., Neville, E. and Walker, A.: Immunology of Sarcoidosis, Am J Med 59:388, 1975.
3. Van Furth, R., ed. *Mononuclear Phagocytes in Immunity, Infection and Pathology*, 2nd edition., Blackwell-Scientific, Oxford, England, 1975.
4. Nelson, D. S., ed. *Immunobiology of the Macrophage*, Academic Press, New York, 1976.
5. Kay, N. E. and Douglas, S. D.: The mononuclear phagocyte: Its Development, Structure, Function and Involvement in the Immune Response, N Y State J Med 77:327, 1977.
6. Hedfors, E., Holm, G. and Pettersson, D.: Lymphocyte Subpopulations in Sarcoidosis, Clin Exp Immunol 17:219, 1974.
7. Huber, H., Douglas, S. D. and Fudenberg, H. H.: The IgG Receptor: An Immunologic Marker for the Characterization of Mononuclear Cells, Immunology *17*:17, 1969.
8. Huber, H., Douglas, S. D., Nusbacher, J.: Kochwa, S. and Rosenfield, R. E. IgG Subclass Specificity of Human Monocyte Receptor Sites, Nature 229:419, 1971.
9. Douglas, S. D., Schmidt, M. E. and Siltzbach, L. E.: Monocyte Receptor Activity in Normal Individuals and Patients with Sarcoidosis, Immunol Commun 1:25, 1972.
10. Douglas, S. D., Schmidt, M. E. and Siltzbach, L. E.: Peripheral Blood Monocyte IgG and C3 Membrane Receptor Activity in Patients with Sarcoidosis, Proc. VIth International Conference on Sarcoidosis. Univ. Tokyo Press, Tokyo, 1974, p. 186.
11. Douglas, S. D., Schmidt, M. E., Daughaday, C. C. and Siltzbach, L. E.: Kinetics of Monocyte Receptor Activity for Immunoproteins in Patients with Sarcoidosis, Ann NY Acad Sci 278:190, 1976.
12. Schmidt, M. E. and Douglas, S. D.: Monocyte IgG Receptor Activity, Dynamics and Modulation – Normal Individuals and Patients with Granulomatous Disease, J Lab Clin Med 89:332, 1977.
13. Schmidt, M. E. and Douglas, S. D.: Disappearance and Recovery of Human Monocyte IgG Receptor Activity after Phagocytosis, J. Immunol. 109:914, 1972.
14. Schmidt, M. E. and Douglas, S. D.: Effects of Synthetic Single-and-Multi-Stranded Polynucleotides on Human Monocyte IgG Receptor Activity in vitro, Proc Soc Exp Biol Med 151:376, 1976.

15. Douglas, S. D.: Human Monocyte Spreading *in Vitro:* Inducers and Effects on Fc and C3 Receptors, Cell Immunol 21:344, 1976.
16. Schmidt, M. E. and Douglas, S. D.: Effects of Levamisole on Human Monocyte Function and Immunoprotein Receptors, Clin Immunol Immunopathol 6:299, 1976.
17. Page, R. C., Davies, P. and Allison, A. C.: Participation of Mononuclear Phagocytes in Chronic Inflammatory Diseases, J. Reticuloendothel Soc 15:413, 1974.
18. King, G. W., Bain, G. and LoBuglio, A. F.: The Effect of Tuberculosis and Neoplasia on Human Monocyte Staphylocidal Activity, Cell Immunol 16:389, 1975.
19. Dannenberg, A. M.: Macrophages in Inflammation and Infection, N Eng J Med 293:489, 1976.
20. Warren, K. S.: A Functional Classification of Granulomatous Inflammation, Ann N Y Acad Sci 278:7, 1976.
21. James, D. G.: The Centenary of Sarcoidosis, Ann NY Acad Sci 278:736, 1976.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Epithelioid Cell and Sarcoid-Like Granuloma. A Review of Human and Experimental Material

P. SOLER, J.-F. BERNAUDIN, F. BASSET, AND G. BASSET

The sarcoid-like granuloma represents a particular immunologic response more or less related to delayed hypersensitivity (1–2). It is defined by strict morphologic features: epithelioid cells, giant cells, and lymphocytes organized as a follicle. The epithelioid cell, its main component, is described on light microscopy as a large cell with fuzzy contours, a slightly acidophil cytoplasm, and an elongated or kidney-shaped nucleus. It was called "epithelioid" because of its epithelial appearance, such a terminology being in fact old and deceptive, but traditionally used.

The human material was obtained from lung, skin and lymph node biopsies of patients with pulmonary sarcoidosis (35 patients), positive Kveim tests (12 patients), tuberculosis (6 patients), hypersensitivity pneumonitis (5 patients) and leprosy (2 patients).

The tissue was immediately fixed for EM by immersion in cold (4°C) 1.7 % glutaraldehyde in cacodylate buffer (pH 7.3) for one hour. After rinsing in cacodylate buffer, the tissue blocks were osmicated, dehydrated and Epon-embedded. Standard procedures were followed for light microscopy. The study of paraffin sections ensured the diagnosis and revealed the presence of epithelioid and giant cell granulomas. Significant fields were selected on semithin sections. Ultrathin sections were contrasted with uranyl acetate and lead citrate (3) and examined in a Siemens Elmiskop 101 EM at 80 KV.

The experimental material was obtained from animals prepared by two 24-hour-interval injections of 0.5 ml/kg CFA into the dorsal tail vein, followed by daily oral aureomycin for 1 week. Twenty-nine female Wistar rats weighing 80 g (9 controls, 20 CFA injected) and 60 mice of 4 different strains (10 AKR, 10 Balb, 10 KK, 10 Swiss, and 4 x 5 controls) were used.

The lungs were fixed in situ and processed for light and electron microscopy as previously described (4).

Sarcoid Granulomas

Ultrastructure of Epithelioid Cells

In all the sarcoid granulomas we studied, the mature epithelioid cells present very similar features. They are large cells (20–40μ) usually elongated, with an eccentric nucleus composed of a thin band of peripheral heterochromatin and a prominent nucleolus. The cell contours are irregular, exhibiting numerous interdigitated, long and slender processes. Cytoplasmic organelles are abundant, suggesting secretory capabilities: well-developed

From the Groupe INSERM U82, Hôpital Bichat, Paris, France.

Golgi apparatus and rough endoplasmic reticulum, numerous mitochondria and many characteristic membrane-bound vesicles (0,3-1 μ) with a thin granular content were noted. A polysaccharidic component is evidenced by the PATAG reaction according to Thiery (5). These vesicles come probably from the Golgi apparatus and are occasionally associated with the plasma membrane, recalling exocytosis.

Morphology of the Granuloma and Cell Distribution

In a recent paper (6) we reported a study on serial sections of a pulmonary sarcoid granuloma using light and electron microscopy which we undertook in order to define more precisely some of its architectural details. The granuloma was composed of two distinct areas separated by a ring of fibroblasts:

A central follicle made of tightly packed cells, mainly epithelioid, associated with a few macrophages, monocytes and lymphocytes.

A peripheral area consisting of a loose collection of collagen fibers and inflammatory cells (mostly lymphocytes), macrophages and monocytes.

In the follicle, individual groups of lymphocytes and monocytes were in close contact with surrounding epithelioid cells. Blood capillaries and lymphatic channels were located in the peripheral area, with only mononuclear cells passing through the walls.

Moreover, in adjacent alveolar spaces, the epithelial lining was disrupted in some places, and cells crossed the basal lamina into alveolar spaces. Some were macrophages, others had characteristics similar to those of altered epithelioid cells. These findings suggested that epithelioid cells may result from modification of mononuclear cells, probably macrophages, and that after their sojourn in the follicle they could be discharged into the alveolus.

Particularity of some Sarcoid Granulomas

On two occasions in lung and lymph node sarcoid material, tubuloreticular structures were found in lymphocytes and endothelial cells, and on one occasion in epithelioid cells as well (7).

The structures consisted of a tight network of hollow tubules (20–22 nm in external diameter) within a dilatation of the rough endoplasmic reticulum, sometimes opened through the reticulum membrane. In some instances the structures might be seen in the perinuclear cisterna. Such structures have already been reported in various diseases. Their nature (viral or other) remains controversial (7).

Morphology of Sarcoid-Like Granulomas

In Human Pathology

The EM study of 12 positive Kveim tests reported in the IVth Conference on Sarcoidosis (8) showed the great similarity between epithelioid cells of original sarcoid lesions and the cells present in the granulomas induced by the "Kveim-Siltzbach antigen."

The epithelioid cells forming tuberculosis granulomas are similar to the sarcoid ones except for some of them which contain periodic myelin-like coils as previously described (9).

In granulomas of hypersensitivity pneumonitis epithelioid cells and giant cells have features similar to those in sarcoidosis. However, they are less numerous than the associated macrophages, unlike sarcoid granulomas where they are the main element (10). Besides, lymphocytes and plasma cells are extremely numerous in hypersensitivity pneumonitis, either in granulomas and in alveolar walls and perivascular sheaths.

In tuberculoid leprosy, the epithelioid cells are similar to the sarcoid ones. On the other hand, the macrophages of lepromatous leprosy, so-called Virchow's cells, are different. They contain bacterial debris in phagolysosomes and many empty vesicles.

In Animals

We studied the ultrastructural changes in the rat lung following the intravenous CFA injection (4), which induced interstitial granulomas consisting of large mononuclear cells. Most of these cells appeared to be macrophages. Their nuclei were usually elongated and kidney-shaped with very prominent nucleoli and intranuclear bodies. Cell contours were irregular, sometimes exhibiting short cytoplasmic processes. Cytoplasmic organelles were numerous. These cells had also phagocytic characteristics: lysosomes, phagolysosomes and numerous vacuoles containing lipid material, sometimes extracted by the processing techniques. The phagolysosomes often contained partially digested CFA mycobacteria.

In light microscopy epithelioid cells appeared to form the major part of granulomas but, except at the periphery of granulomas, their ultrastructural characters differed from those observed in human granulomas. In contrast to the more central cells, they possessed relatively few lysosomes and phagolysosomes. They contained small membrane-bound vesicles with a thin granular content, similar to the characteristic vesicles of the human epithelioid cell. Their plasma membrane showed long thin digitations.

We attempted to induce a pulmonary granulomatosis in mice of four different strains, to investigate whether a genetic factor was involved in the production of such lesions. Although we used the same protocol as for rats, the animals of the four strains (Swiss, AKR, KK and Balb) never developed interstitial granulomas; at most they had some insignificant inflammatory infiltrates.

The negative results are probably due to the difference in animal species; the technique successfully used in rats was not suitable for mice, or CFA was ineffective in mice.

Comments

Epithelioid and giant cells are known to be derived from cells belonging to the mononuclear phagocyte system. In vitro, Sutton and Weiss (11) have obtained epithelioid cells from peripheral avian blood monocytes in cell cultures. In vivo, Epstein (12) has shown that labeled monocytes are found later as epithelioid cells in granulomas induced by zirconium salts. By implanting cellophane strips into mice, Papadimitriou and Spector (13) obtained cells that were indistinguishable from the epithelioid cells and the macrophage precursors labeled in bone-marrow could be identified as epithelioid cells in these cellophane-induced granulomas.

The factors that induce the transformation of macrophages into epithelioid cells remain uncertain. Papadimitriou and Spector (13) suggest that epithelioid cells develop from macrophages mobilized at a site of inflammation. These macrophages turn into epithelioid cells only if there is little to ingest or if the ingested material is already thoroughly digested and has been reduced to soluble substance. Uptake of indigestible and non excretable material prevents macrophages from becoming epithelioid cells. In experimental pulmonary granulomatosis induced in rats by intravenous CFA, the histiocytes that are the main component of the granulomas are not epithelioid cells; the lack of transformation may be explained by the indigestibility of CFA-mycobacteria. In human sarcoid lesions, no organic or mineral foreign body is found in the follicles, either within cells or between them.

The transformation of macrophages into epithelioid cells may be induced by antigenic materials, such as eggs of Schistosoma mansoni. For Warren (14) the inhibition of these events in conditions characterized by the suppression of cell-mediated reactions suggests that surrounding lymphocytes take part in the process. Tannenbaum et al, (15) using immunomorphologic methods have shown that the populations of lymphocytes are not only composed of T lymphocytes but also of B lymphocytes, suggesting that humoral components also play a role in the formation of such granulomas.

The function of epithelioid cells is unclear. These cells have some ultrastructural characteristics of secretory cells possessing well-developed rough endoplasmic reticulum and Golgi apparatus. Their membrane-bound vesicles may come from the Golgi apparatus and we found a few images of excretion. On the other hand no phagosomes or phagolysosomes exist in these cells. Epithelioid cells seem to have lost their phagocytic ability although they are very active in pinocytosis. Epithelioid cells are macrophages committed to secretion rather than to phagocytosis.

The cell's secretions, which have a polysaccharidic component, are not yet fully determined. The presence of high levels of angiotensin-converting enzyme (ACE), not only in serum of patients, but also in a sarcoid lymph node, suggests to Lieberman (16) that this enzyme is probably one of the secreted products. According to Valerie-James and Jones Williams (17), these products could play a role in the formation and persistence of granulomas.

In BCG and CFA induced granulomas, where centrally located macrophages contain bacteria or phagocytosed irritant particles, epithelioid cells are found in the peripheral area only, suggesting to Papadimitriou and Spector (13) that epithelioid cells could play a role in digesting, detoxifying or excreting toxic substances released from the central cells of the granuloma.

References

1. Epstein, W. L.: Granulomatous Hypersensitivity. In *Progress in Allergy,* Volume II. Karger, Basel and New York, 1967, pp. 36–88.
2. Spector, W. G.: Chronic Inflammation. In *The Inflammation Process,* vol 3 (2nd edition). Edited by G. Mc Cluskey - Academic Press, New York and London, 1974, pp. 277–289
3. Venable, J. H. and Coggeshall, R.: A Simplified Lead Citrate Stain for Use in Electron Microscopy, J Cell Biol 25:407–408, 1965.
4. Soler, P., Bernaudin, J. F., and Basset, F.: Ultrastructure of Pulmonary Granulomatosis Induced in Rats by Intravenous Complete Freund's Adjuvant, Virchows Arch (Path, Anat and Histol) 368:35–50, 1975.
5. Thiéry, J. P.: Mise en Évidence des Polysaccharides Sur Coupes Tines en Microscopie Électronique, J Microsc (Oxf) 6:987–1018, 1967.
6. Soler, P., Basset, F., Bernaudin, J. F., and Chretien, J.: Morphology and Distribution of the Cells of a Sarcoid Granuloma: Ultrastructural Study of Serial Sections, Ann NY Acad Sci 278:147–160, 1976.
7. Bernaudin, J. F., Soler, P., and Basset, F.: Structures Tubulo-Reticulaires Intracytoplasmiques dans Deux Sarcoïdoses et Deux Mesothéliomes Pleuraux malins, Path Europ 8:277-285, 1973.
8. Basset, F., Collet, A., Chretien, J., Normand-Reuet, C. and Turiaf J.: Etude Ultramicroscopique des Cellules de la Réaction de Kveim, In: La Sarcoïdose Rapp. IV Conf. Intern., p. 89–109 - Paris Masson Edit. 1967.
9. Bernaudin, J. F., Soler, P., Basset, F., and Chretien, J.: La Cellule Épithelioide—Données Ultrastructurales au Cours de Diverses Entités Pathologiques Humaines, Pathol Biol 23:494–498, 1975.
10. Basset, F., Le Crom, M, and Decroix G.: Etude Ultrastructurale d'une Biopsie Pulmonaire au Cours D'une Maladie des Éleveurs d'Oiseaux, Pneumopathie Interstielle d'Hypersensibilité, Presse Med 78:699–704, 1970.
11. Sutton, J. S. and Weiss, L.: Transformation of Monocytes in Tissue Cultures into Macrophages, Epithelioid Cells and Multinucleate Giant Cells. An electron Microscope Study, J Cell Biol 28:303–332, 1966.
12. Epstein, W. L.: Granulomatous Hypersensitivity, Prog Allergy 11:36–87, 1967.
13. Papadimitriou, J. M. and Spector, W. G.: The Origin, Properties and Fate of Epithelioid Cells, J Pathol 105:187-203, 1971.
14. Warren, K. S.: A Functional Classification of Granulomatous Inflammation, Ann NY Acad Sci 278:7–18, 1976.
15. Tannenbaum, H., Rocklin, R. E., Schur, P. H., and Sheffer, A. L.: Immunological Identification of Subpopulations of Mononuclear Cells in Sarcoid Granulomas, Ann NY Acad Sci 278:136–146, 1976.
16. Lieberman, J.: The Specificity and Nature of Serum-Angiotensin-Converting Enzyme (serum ACE) Elevations in Sarcoidosis, Ann NY Acad Sci 278:488–497, 1976.
17. Valerie-James, E. M. and Jones Williams, W.: Fine Structure and Histochemistry of Epithelioid Cells in Sarcoidosis, Thorax 29:115–120, 1974.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

HLA Antigens and Disease

EDMUND NEVILLE, M.B., M.R.C.P.

Organ transplantation has achieved widespread success since the observation that foreign tissue rejection is greatly delayed if donor and recipient are "compatible." This compatibility depends on genetically determined antigens on the surfaces of cells throughout the body and these antigens are most conveniently determined on the leucocytes of peripheral blood. They have been termed human leucocyte A (HLA) antigens and the genes controlling the inheritance of these antigens are known as "histocompatibility genes."

Major Histocompatibility Complex

The HLA antigens are determined by two distinct methods—serologic and by lymphocyte interaction in culture. The serologic approach detects cell-surface antigens by means of a panel of internationally validated antisera. Computers have satistically analyzed the reaction pattern of large numbers of patients' leucocytes and three antigens have been defined: HLA - A, B, and C. Human leucocyte A antigens - A and B have received most attention and after population and family studies have been shown to be controlled by genes of a single genetic region. The loci on this region are separable by genetic recombination between parent and off-spring. The second method of lymphocyte typing, that of mixed lymphocyte reaction in culture (HLA - D) is also controlled from the same genetic region. This genetic region is known as the major histocompatibility complex (1) and is found on the sixth chromosome (Fig. 1).

The four types of HLA antigens are all found on the surface of T lymphocytes. Separate B lymphocyte alloantigens are now being determined by similar methods though an international standardization of antisera has yet to be agreed.

Animal Studies

Most knowledge of the genetics of the HLA antigens are based on animal experiments. The concept of the major histocompatibility complex derived from a mouse model. In mice the genetic area controlling leucocyte antigens is also responsible for specific immune responses; and mice inheriting particular leucocyte antigens have an increased susceptibility to specific diseases—autoimmune thyroiditis, acute lymphocytic choriomeningitis, and virus induced leukemia. Theories to explain histocompatibility antigen association with disease are also based on animal studies. The histocompatibility antigens may be closely associated with immune-response genes and so may not be directly involved in disease pathogenesis or, alternatively, the anti-

From the Royal Northern Hospital, London, England.

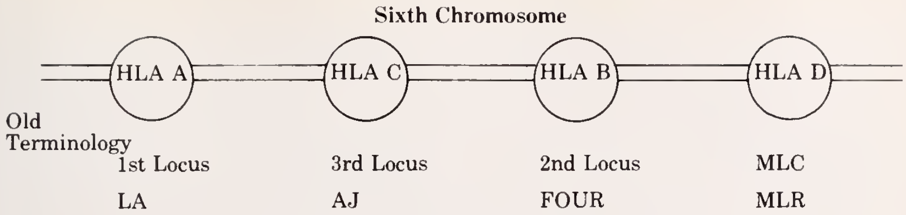

FIG. 1. Major histocompability complex.

gens may cross-react with foreign protein, inducing tolerance, or act as receptors for foreign antigens, such as viruses.

The disease-histocompatibility association in mice led to a similar search in man. Many diseases have now been linked to different HLA antigens, though, the most significant associations are with B group antigens and notably B27 (Table I).

HLA B27

Ankylosing spondylitis

Many diseases have been investigated for association with HLA antigens but none have shown such a convincing link as ankylosing spondylitis and HLA B27. The initial reports by Brewerton et al in London (2) and Schlosstein et al in Los Angeles (3) were that B27 was present in 72 of 75 (96 %) and 35 of 40 (86 %) Caucasian adults, compared with 8 % of the control population. Since then there have been many confirmatory reports, although it is apparent that classic ankylosing spondylitis can develop in the absence of B27. B27 is not sex linked, so that the sex incidence of ankylosing spondylitis is not explained, and most individuals with B27 have no clinical evidence of spondylitis. Clearly there are other factors involved which may be both genetic and environmental and so far remain undiscovered.

Sero-Negative Arthropathies

Ulcerative colitis, Crohn's disease, psoriasis, nonspecific urethritis, Salmonella or Yersinia enterocolitica infections are not themselves associated with a particular HLA antigen. However, when an arthritis is present with any of these diseases or when Reiter's disease follows urethritis or Shigellosis then B27 is found in at least 30 % of patients. If sacroiliitis or ankylosing spondylitis is present then B27 increases to 75 % or more.

Acute Anterior Uveitis

Acute anterior uveitis may occur on its own or be associated with ankylosing spondylitis, Reiter's disease, ulcerative colitis, Crohn's disease or Yersinia arthritis, though not with psoriasis or psoriatic arthropathy. Fifty-eight of 100 patients in London with acute anterior uveitis had B27. This included 29 of 67 (43 %) with no associated disease (4).

TABLE I

Clinical Associations with HLA-B27 and B8

Disease	% B27	Disease	% B8
Ankylosing Spondylitis	90	Myasthenia Gravis	60
Crohn's Arthritis	75	Graves Disease	47
Ulcerative Colitis Arthritis	75	Addison's Disease	69
Reiter's Disease	75	Chronic Active Hepatitis	60
Yersinia and Salmonella Arthritis	90	Coeliac Disease	78
Psoriatic Arthropathy	30	Dermatitis Hepetiformis	62
Acute Anterior Uveitis	58	Sarcoid Arthritis	82
Asbestosis	32	Sarcoid Erythema Nodosum	58
Frozen Shoulder	42		

Other Conditions

Of 56 asbestos workers suspected to have asbestosis, 19 had moderate to severe pulmonary asbestosis. Six (32 %) had B27, suggesting that B27 may be a useful marker of increased susceptibility to the tissue-damaging effects of asbestos dust (5).

HLA B8

Most of the autoimmune disorders have been investigated for an association with HLA antigens and the majority have some link with B8. In myasthenia gravis, Graves disease, Addison's disease and chronic active hepatitis this link is firmly established. However, the archetype of autoimmune disease, systemic lupus erythematosus, is not associated with B8. Early reports only achieved borderline significance and have not been confirmed (6). Similarly the B8 association in myasthenia is with younger female patients and not with those possessing autoantibodies. Hence B8 is not related to the autoimmune process itself. Gluten-sensitive entero-pathy and dermatitis herpetiformis are not generally held to be autoimmune disorders and are also associated with B8.

HLA D

Two HLA antigens such as A1 and B8 may be found together more frequently than statistically predicted. This is known as a linkage dysequilibrium. The D locus is adjacent to the B locus and so it is not yet known whether a linkage dysequilibrium may exist between D and B locus antigens. Nevertheless preliminary reports have shown increased D locus antigens in association with rheumatoid arthritis, diabetes mellitus, multiple sclerosis, and celiac disease.

Miscellaneous Diseases

The list of diseases linked with HLA antigens is constantly extending (7, 8). Definite associations are insulin dependent diabetes mellitus (B8, BW 15, DW 2, DW 4), multiple sclerosis (A3, B7, B18, DW 1, and a distinct B lymphocyte alloantigen), psoriasis (B13, BW 17), Hodgkin's disease (A1, B5, B 18), acute lymphatic leukaemia (B12). Many other associations have been reported and some await confirmation. Different manifestations of diseases are now being examined for relationship to HLA antigens. Hence the need for surgery in rheumatic heart disease may be related to HLA antigens. Different etiologies of glomerulonephritis may be related to different HLA antigens, i.e., differing patient susceptibilities. The response to steroids in the nephrotic syndrome may be predicted by a knowledge of the patients' HLA antigen.

Sarcoidosis

Sarcoidosis itself is not associated with a particular HLA antigen (9, 10), although patients with B7 have been reported to be more likely to retain a negative tuberculin response and to become asymptomatic (10). Particular features of sarcoidosis have not previously been analyzed. Both seronegative arthritis and anterior uveitis are known to be HLA-linked and both are features of sarcoidosis. Groups of patients with anterior uveitis, arthritis, erythema nodosum, arthritis combined with erythema nodosum, lupus pernio, and bone disease have been examined separately. All had histologically proven sarcoidosis.

In a series of 115 patients there was no overall perturbation of frequency of HLA antigens (Table II). However, B8 was significantly associated with sarcoid arthritis and erythema nodosum whether alone or in combination. Because of the linkage dysequilibrium between A1 and B8, A1 was increased in association with arthritis. Statistically there were some other increased frequencies. BW 21 (P=0.046) and B 27 (P=0.016) with arthritis and erythema nodosum; BW 22 (P=0.011) with arthritis alone; BW 21 (P=0.0026) with bone sarcoid; and B 13 (P=0.0084) with lupus pernio. All of these

TABLE II

HLA Antigens in Relation to Clinical Features of 115 Patients with Sarcoidosis

Manifestations of Sarcoidosis	Patients Studied		A1			B8			B27			B7		
	No.	%	No.	%	p	No.	%	p	No.	%	p	No.	%	p
Overall	115	100	46	40	N.S.	47	41	N.S.	10	9	N.S.	35	31	N.S.
Anterior Uveitis	56	49	22	39	N.S.	16	29	N.S.	3	5	N.S.	20	36	N.S.
Erythema Nodosum	12	10	4	33	N.S.	7	58	0.02	1	8	N.S.	5	42	N.S.
Erythema Nodosum Arthritis	12	10	6	50	N.S.	9	75	0.0012	3	25	0.016	2	17	N.S.
Arthritis	11	10	7	64	0.032	9	82	0.0004	1	10	N.S.	2	20	N.S.
Lupus Pernio	13	11	6	46	N.S.	5	38	N.S.	2	15	N.S.	2	15	N.S.
Bone	12	10	6	50	N.S.	5	42	N.S.	1	8	N.S.	2	17	N.S.
Mantoux Negative	73/92	79	31	42		33	45		6	8		23	32	
Chest Radiograph Resolution	56/98	57	18	33		28	51		5	9		20	36	
Controls	1300			28			27			8			27	

N.S. = not significant. Significance is calculated from a Z variate from the normal approximation to the binomial difference between two populations.

associations must be regarded as extremely doubtful on account of small numbers (only two patients in some cases). B7 was not particularly associated with a negative tuberculin or with chest radiograph resolution.

The association of B8 both with arthritis and erythema nodosum indicates that individuals with this antigen are prone to develop these manifestations of sarcoidosis. It is not unreasonable to suppose that other, as yet unidentified, antigens predispose a patient with sarcoidosis to most, if not all, individual manifestations of the disease. Most important is the presence of B27 in only 5 % of patients with anterior uveitis associated with sarcoidosis, which is in sharp contrast to the findings at Westminster Hospital that B27 was present in 43 % of patients with acute anterior uveitis who had no evidence of an associated disease and in 86% of patients who had uveitis associated with ankylosing spondylitis, Reiter's disease and other disorders (4). Clinically the types of uveitis associated with B27 are similar to the uveitis of sarcoidosis, and it might have been expected that it too would be related to B27. The absence of such an association in sarcoidosis is difficult to interpret because there are several plausible explanations. The uveitis of sarcoidosis might be a distinct entity despite its clinical similarity; the 43 % of patients with B27 and uveitis alone might represent a forme fruste of ankylosing spondylitis without rheumatic disease; or there might be genetic factors predisposing to uveitis which are associated with B27 in some circumstances but not in others.

Conclusion

The discovery of the HLA antigen system and its relationship not only to diseases but to individual manifestations of specific diseases is a major contribution to our understanding of pathogenesis and personal susceptibility to disease states. The association of particular syndromes with serologically determined antigens of A and B type point the way to the major advance in understanding of disease that will follow when this preliminary work is combined with the study of HLA D loci and the B lymphocyte alloantigens.

Acknowledgments

The sarcoidosis study was performed under the supervision and guidance of Dr. D. Geraint James at the Royal Northern Hospital. I am grateful to Dr. D. A. Brewerton, Dr. D. C. O. James, Miss C. Cockburn, and Miss B. Fenichal at Westminster Hospital who performed the tissue typing and supplied the statistics.

References

1. Bach, F. H., and van Rood, J. J.: The Major Histocompatibility Complex—Genetics and Biology, N Engl J Med 295:806, 1976.
2. Brewerton, D. A., Caffrey, M., Hart, F. D., James, D. C. O., Nicholls, A., and Sturrock, R. D.: Ankylosing Spondylitis and HLA-27, Lancet 1: 904, 1973.
3. Schlosstein, L., Terasaki, P. L., Bluestone, R., and Pearson, C. M.: High Association of an HL-A Antigen, W27, with Ankylosing Spondylitis, N Engl J Med 288:704, 1973.

4. Brewerton, D. A.,: HL-A 27 and Acute Anterior Uveitis, Ann Rheum Dis 34: Suppl 1, 33, 1975.
5. Merchant, J. A., Klouda, P. T., Soutar, C. A., Parkes, W. R., Lawlers, S. D., Turner-Warwick, M.: The HL-A System in Asbestos Worker, Br Med J 1:189, 1975.
6. Kissmeyer-Nielsen, F., Kjerbye, K. E., Andersen, E., and Halberg, P.: HL-A Antigens in Systemic Lupus Erythematosus, Transplant Rev 22:164, 1975.
7. Dausset, J., Degos, L., and Hors, J.: The Association of the HL-A Antigens with Disease, Clin Immunol & Immunopathol 3:127, 1974.
8. Svejgaard, A., Platz, P., Ryder, L. P., Nielsen, L. S., and Thomsen, M.: HL-A and Disease Associations—A Survey, Transplant Rev 22:3, 1975.
9. Hedfors, E. and Möller, E.: HL-A Antigens in Sarcoidosis, Tiss Antigens 3:95, 1973.
10. Persson, I., Ryder, L. P., Nielsen, L. S., and Svejgaard, A.: The HL-A Histocompatibility Antigen in Sarcoidosis in Relation to Tuberculin Sensitivity, Tiss Antigens 6:50, 1975.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Sarcoid Granulomas Associated with Phenylbutazone Treatment

E. G. LEBACQ AND V. DESMET

In addition to numerous toxic reactions, phenylbutazone can induce various hypersensitivity manifestations, such as lupus-like syndrome, lymph node enlargement, and lung disorders. A case is reported of a patient with sarcoid-like involvement of the liver and the lungs, apparently ascribable to phenylbutazone treatment.

Case Report

The patient 45-year-old, suffering from low back pain following a railway accident, was treated with phenylbutazone, for the first ten days parenterally 1 g per day, and for the next three weeks orally at the dose of 300 mg per day. The total amount of the drug she received was approximately 16 g over one month.

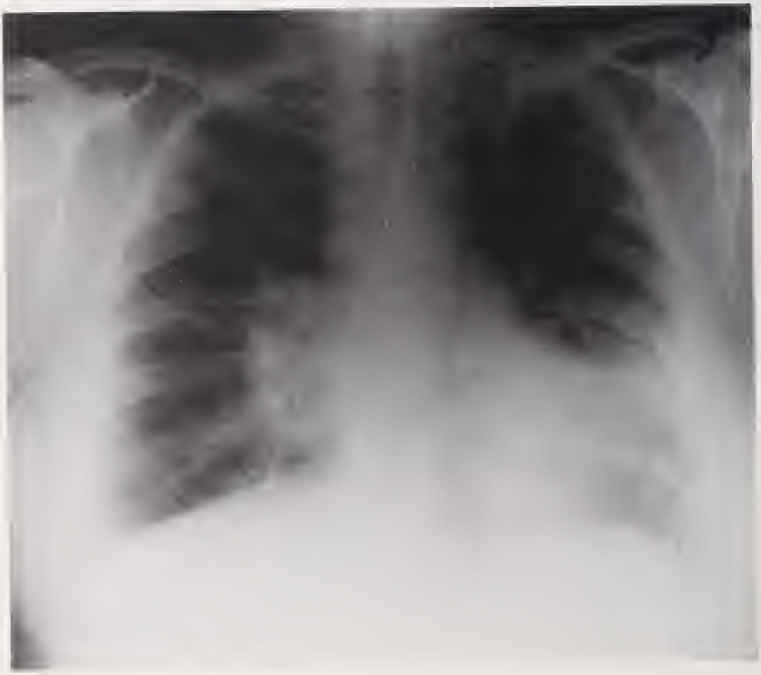

FIG. 1. Diffuse shadows in both lungs.

At the time she had intense dyspnea, generalized erythematous rash, and fever.

Chest x-ray revealed diffuse shadows in both lungs (Fig. 1).

From the Department of Internal Medicine, University of Louvain Medical School, and the Laboratory of Histopathology, Hôpital de Jolimont, Belgium.

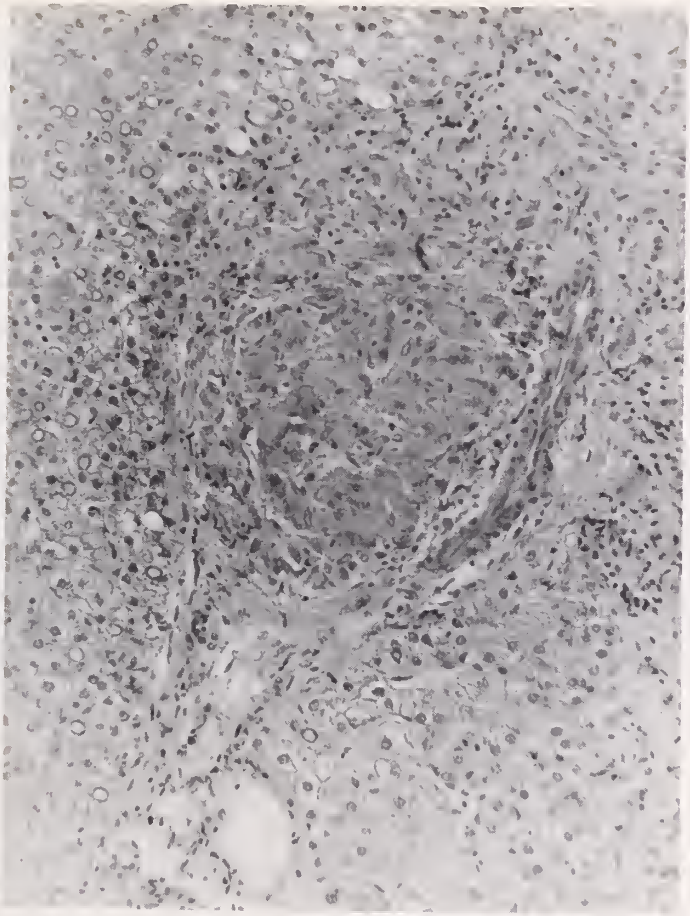

FIG. 2. Liver-punch biopsy.

The liver and the spleen were enlarged; there were no palpable lymph nodes. Tuberculin reaction was weakly positive. Laboratory data showed an inflammatory reaction, a polyclonal gammopathy, leukopenia (WBC: 2.700/μL), with normal RBC and platelets. No LE cells, no fluorescent antinuclear antibodies, or other autoantibodies were detected. There were no acid-fast bacilli found in the sputum. Blood calcium, or phosphorus, bilirubin, BSP retention, and various enzymes were normal, except for alkaline phosphatase elevated at 260 mU/ml.

Liver-punch biopsy revealed numerous sarcoid granulomas (Fig 2).

In spite of considerable improvement of the dyspnea after one week of prednisone treatment, the chest x-ray was unchanged and a surgical lung biopsy was performed, which showed a granulomatous reaction. The epithelioid granulomas were shown to be poorly demarcated, surrounded by numerous inflammatory cells scattered in the interalveolar septa. Alveolar spaces were largely unaffected (Fig. 3).

Serologic tests for brucellosis, ornithosis, toxoplasmosis, and various common viruses of the respiratory tract were all negative.

Intradermal and patch tests with varying dilutions of aqueous phenylbutazone gave rise to similar inflammatory reaction in the patient and the controls.

An agar-plate diffusion test failed to show specific precipitins against phenylbutazone in the serum of the patient.

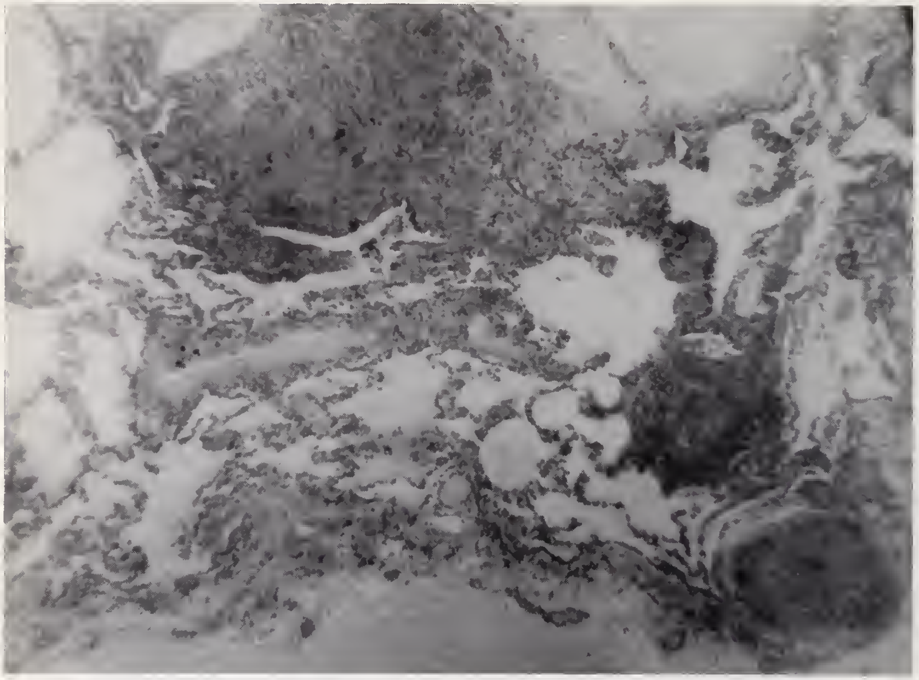

FIG. 3. Surgical lung biopsy showed granulomatous reaction. Epithelioid granulomas poorly demarcated, surrounded by numerous inflammatory cells scattered in the interalveolar septa. Alveolar spaces were largely unaffected.

After six weeks of prednisone treatment, the chest radiography was practically normalized, and the spleen was no longer palpable.

The treatment was stopped and a Kveim test carried out at the time was negative one month later.

Various clinical and biologic controls performed three months later and twice a year for the following three years were unremarkable.

Comments

The diagnosis of tuberculosis, sarcoidosis, and various infectious diseases capable of inducing granulomatous reactions in the liver and the lungs was discarded on clinical and biologic grounds.

Phenylbutazone was the only therapeutic agent to be incriminated and the simultaneous occurrence of a rash and moderate leukopenia without autoimmune laboratory features seems to show additional evidence of the responsibility of this drug.

The pulmonary aspects of the case published by Thurston et al (1) are apparently similar to those of our patient, but there was no lung histology available and the granulomatous nature of the reaction is not established.

The patient of Goldstein (2) had granulomatous involvement of lymph nodes, liver and spleen, but no pulmonary changes.

Sulfonamides and phenylbutazone are the only drugs cited by Guckian and Perry (3) able to give rise to granulomatous hepatitis.

Hypersensitivity is probably responsible for this kind of reaction, although we were unable to prove it. Goldstein (2) noted positive cutaneous tests to phenylbutazone in his patient although no specific precipitins could be demonstrated.

References

1. Thurston, J. G. B., Marks, P. and Trapnell, D.: Lung Changes Associated with Phenylbutazone Treatment, Br Med J 4:1422, 1976.
2. Goldstein, G.: Sarcoid Reaction Associated with Phenylbutazone Hypersensitivity, Ann Intern Med 59:97, 1963.
3. Guckian, J. C. and Perry, J. E.: Granulomatous Hepatitis. An Analysis of 63 Cases and Review of the Literature, Ann Intern Med 65:1081, 1966.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

The Prognosis and Management of Sarcoidosis

CAROL JOHNSON JOHNS

The natural history of sarcoidosis is known for the spontaneous remissions which may be permanent with little or no evidence of residual damage, as well as relentless progressive inflammation with damaging fibrosis and impaired organ function (1–5). There are infinite gradations between, the degree of impairment depending on the location and extent of involved tissues. Because of the observed spontaneous remissions, a period of several months of observation of the course of the disease is indicated whenever possible. In some circumstances, serious life-threatening or functionally incapacitating disease may demand prompt treatment. Aggressive efforts to obtain previous chest radiographs often provide added information about the onset of pulmonary disease or mediastinal adenopathy.

Disease Onset

An asymptomatic incidental finding of bilateral hilar adenopathy is a frequent mode of patient identification. Right paratracheal adenopathy often is present. Patients without symptoms or abnormal physical findings do not require treatment and the vigor of diagnostic efforts should not exceed the gravity of the manifestations. A spontaneous remission is very likely to occur in such patients within one to two years and there is debate about whether it is necessary to obtain histologic support for the diagnosis (6). The diagnostic possibility of lymphoma is often of concern, but no documented cases of lymphoma have been identified with the initial presentation of asymptomatic symmetrical bilateral hilar adenopathy. The appearance of unilateral hilar adenopathy must always arouse suspicion of disease other than sarcoidosis, although this has been noted at some stage in a few cases.

A gradual onset of symptomatic disease is common, with constitutional symptoms and findings related to specific organ involvement. Pulmonary disease is the most frequent, with symptoms often noted over periods of three to twelve months prior to definitive diagnosis. Cervical lymphadenopathy, ocular disease, and hepatic disease are frequent presenting manifestations. The more extensive and severe the involvement, the less likely a spontaneous remission seems. The need for treatment depends on the degree of present or anticipated functional impairment and the severity of associated constitutional symptoms. For example, lymphadenopathy or skin changes may be persistent but are not responsible for serious impairment.

The abrupt onset of erythema nodosum with characteristic pretibial skin changes, fever, arthralgias, and hilar adenopathy is a well-recognized clinical syndrome that may indicate sarcoidosis. In such patients, a spontaneous remission will occur within a few weeks or months in a high precentage of

From the Department of Medicine, Johns Hopkins University, Baltimore, Md. 21205

patients. In the interim, simple salicylate therapy often will provide symptomatic relief. This picture is most frequently noted in white females, but has been identified in black females, and occasionally in males as well. However, in some patients, active ocular disease and extensive pulmonary infiltrates or significant hepatic disease may also be present and a spontaneous remission is then very infrequent and treatment is required.

Diagnostic Histology

Histologic support for the diagnosis is always needed if treatment is contemplated. Other recognized causes of granulomatous disease must be excluded. Evidence of clinical involvement of more than one organ system is necessary to support the diagnosis of this systemic disease and avoid confusion with local sarcoid tissue reactions. The indicated biopsy is that which combines the least risk with the greatest likelihood of diagnostic yield. Superficial or palpable lesions of skin, lymph nodes, and conjunctiva often are readily and easily obtained. Transbronchial lung biopsies (7) or mediastinoscopy will be productive in almost all patients with significant lung and/or node involvement. Liver biopsies reveal granulomas in 70–80 percent of these patients, even without clinical evidence of hepatic disease, but the significance must be interpreted in the light of the entire clinical picture. It is well known that the characteristic histologic picture of noncaseating granulomas is never pathognomonic, regardless of the origin of the tissue. The amount of histologic support required varies inversely with the certainty with which the pattern of clinical features is recognized. The usefulness of the Kveim reaction in providing histologic support is discussed elsewhere.

Pulmonary Function Measurements

These serve as important indicators of severity of involvement, progression, response to treatment and relapse. Simple noninvasive measurements of forced and timed vital capacity can be repeated without major expense or discomfort to the patient and correlate well with other clinical parameters. A single measurement cannot distinguish active and at least partially reversible disease from inactive and irreversible pulmonary fibrosis. Measurements of resting diffusing capacity reflect loss of effective alveolocapillary-diffusing surface but are subject to distortion by changes in breathing patterns. Mild hypoxia is often seen, but arterial blood gases are rarely necessary to follow the course of the disease. Airway obstruction is usually not a clinical feature except in late extensive disease with peribronchial fibrosis or with significant endobronchial disease. Restriction, decreased compliance and abnormalities of distribution of ventilation and perfusion result from the pulmonary infiltrates and fibrosis.

Treatment Effects

Adrenal corticosteroids can suppress dramatically the active inflammatory reaction and provide important symptomatic and functional improvement. A favorable effect on the long term prognosis is suspected but difficult to prove without matched control series (8, 9, 10). It is unlikely that such a controlled series can be achieved in symptomatic incapacitating disease and at the other end of the spectrum, asymptomatic mild disease does not justify treatment. However, study of patients before, during and after treatment may allow the patients to serve as their own controls. Treatment indications and effects vary with the specific disease manifestations as described below.

Pulmonary Disease

Intrathoracic sarcoidosis has been described according to the radiographic pattern in the following groups or "stages," although it is not clear that patients progress through these "stages."

Stage 1. Bilateral hilar adenopathy without grossly visible parenchymal changes
Stage 2. Bilateral hilar adenopathy with pulmonary infiltrations
Stage 3. Pulmonary infiltrations without hilar adenopathy.

The most favorable prognosis is with hilar adenopathy alone and the least favorable is when significant pulmonary fibrosis is present.

Pulmonary sarcoidosis varies greatly in its manifestations and severity, but is the most frequent indication for corticosteroid treatment. The prognosis of an individual patient depends on the race, the extent of disease and the need, use and adequacy of treatment and the compliance with the regimen. When a spontaneous remission occurs, relapse and further problems are unlikely. An optimistic approach is well justified when the patient initially does not seem seriously incapacitated, as reflected by symptoms, radiographic patterns and measurements of pulmonary function.

It is generally agreed that seriously ill patients with incapacitating cough and dyspnea and significant radiographic and pulmonary function changes do require corticosteroid treatment. There is further agreement that asymptomatic patients with normal lung functions and hilar adenopathy without radiographic evidence of parenchymal lung disease do not require treatment unless the disease progresses and changes. In between is an area of uncertainty requiring careful observation for clues of remission or progression that must be identified in order to determine rationally the need for treatment. A discrepancy between widespread significant radiographic changes and minimal symptoms is often characteristic. However, even in the absence of obvious parenchymal lung changes, there may be reduction in measurements of ventilation and diffusion. Characteristic granulomatous changes were demonstrated in the lungs of those who appeared to have only hilar adenopathy when a series of patients was routinely submitted for lung biopsy (11). In some patients, most frequently white, there may be extensive radiographic changes with minor or no symptoms and with vital capacity and diffusing capacity measurements within the normal range. In some of these, irreversible incapacitating pulmonary fibrosis later may ensue. Progressive incapacitating disease seems more frequent in black patients but unequivocal benefit from steroids with radiographic clearing, improvement in pulmonary function, and relief of symptoms is well documented both in black and white patients.

Treatment patterns with adrenal corticosteroids have been studied most extensively in pulmonary disease. Table I reveals a recommended regimen with prednisone which has been followed in many patients (10). It does not appear necessary to use more than 40 mg of prednisone daily. Maintenance doses of 10–15 mg daily are usually sufficient and should be maintained for six to eight months (some clinicians recommend an initial period of treatment of two years). Alternate day equivalent doses may be satisfactory when the active process is brought under control and the picture stabilized. Dose reductions of 2.5 mg at two week or monthly intervals can be attempted when the picture appears stable. It is important to follow the patient at least monthly during and immediately after the tapering period, as clearcut relapse occurs in about two-thirds of the patients, usually within a month or two of cessation of treatment (or at any dose below 15 mg daily). Recurrent and reversible relapses have been documented even after more than ten years of treatment but seem to be prevented by low-dose maintenance treatment. Relapses are not subtle and usually are easily identified by the reappearance or worsening of symptoms and radiographic and pulmonary function changes. Reinstitution of treatment, or increased dose produces prompt improvement. It is often possible to return only to the low maintenance dose of 10–15 mg of prednisone which had been sufficient to maintain improvement in the past. Higher doses may be required when relapse has progressed to a more dramatic extent. With recurrent relapses, there is a tendency toward progressive loss of lung function. This is complicated by the fact that recurrent pulmonary infections (bacterial, viral, and fungal) may occur.

Corticosteroids are not a perfect treatment but dramatic benefits may be demonstrated with relatively infrequent and manageable side effects. The vital capacity improves significantly in three-quarters of the patients and the diffusing capacity in one-third of the patients. Mild residual changes are common even though the patient may be entirely free of symptoms. The diffusing capacity rarely returns to normal. The most frequent side effect of steroid treatment is that of excessive weight gain. The relatively young adult ages of patients with sarcoidosis decrease the incidence of osteoporosis, but aseptic necrosis of the femoral head is occasionally encountered. Fungus balls, most commonly with *Aspergillus fumigatus*, may be identified when

TABLE I

Prednisone Treatment Schedule

40 mg, 30 mg (divided doses)	2 wks each	6½ mons
25 mg, single 8 A.M. daily dose	2 wks	
20–15 mg, single 8 A.M. daily dose	5 mons	
12.5, 10.0, 7.5, 5.0, 2.5 mg	2 wks each	2½ mons
Careful observation during tapering		
Retreat if relapse occurs.		
Alternate day equivalents for maintenance and tapering, if desired.		

the fibrocystic changes provide the optimal environment for these saprophytic fungi. Corticosteroid treatment may be a factor in their development but continued treatment is often required. However, invasive aspergillosis is rare and multiple fungus balls may persist and fluctuate in size over many years, with small recurring hemoptyses. Massive hemoptyses are observed infrequently. Surgical resection of such fungus balls is not recommended because of their multiplicity and the associated underlying diffuse restrictive lung disease.

The long-term course of steroid-treated pulmonary sarcoidosis is that of permanent remission in about one-third of the patients. But approximately half may require long-term treatment for many years because of recurrent relapses when treatment is withdrawn. Lifetime treatment may be required for such patients. Disabling pulmonary disease is characterized by recurrent pulmonary infections and pulmonary fibrosis which may culminate in pulmonary insufficiency and cor pulmonale. Death related to the sarcoidosis occurs in 2–10%, most frequently due to pulmonary insufficiency.

Peripheral Lymphadenopathy

Diffuse and usually symmetrical involvement of peripheral lymph nodes is common and usually accompanied by mediastinal and hilar adenopathy. Massive nontender, firm nodes may be widely distributed in the cervical, axillary, epitrochlear and femoral areas, without other symptoms. Biopsy reveals the characteristic findings of noncaseating granuloma, though fibrinoid necrosis is occasionally noted, especially where the disease is accompanied by fever. Node involvement alone is not sufficient indication for treatment, and gradual remission may occur spontaneously over periods of months or years. When adrenal corticosteroids are used, there is prompt and dramatic regression of the nodes.

Ocular Disease

Slit-lamp examination is recommended for all patients to identify evidence of iridocyclitis which is often an early manifestation requiring prompt treatment. Local steroid treatment may suffice but posterior disease with retinal periphlebitis or optic neuritis will require systemic steroids. Eye disease may progress to glaucoma, cataract formation, and blindness. Keratoconjunctivitis sicca resulting from lacrimal gland involvement can be managed with artificial tears. Conjunctival nodules may provide a source for histologic support.

Hepatic Disease

An active hepatic granulomatous process with significantly elevated alkaline phosphatase (but little or no elevation of bilirubin) is accompanied by constitutional symptoms of weight loss, anorexia and fever, and may be a major indication for corticosteroid treatment. Intense pruritis is often a feature. Mild to moderate disease is likely to show prompt clinical improvement, though relapse may occur whenever the corticosteroid dose is lowered.

A marked Cushingoid state ensues more frequently than with pulmonary disease and diabetes frequently develops. A picture resembling biliary cirrhosis may appear and the diagnosis may be difficult and depend on other evidences of sarcoidosis. In some patients the liver disease is the dominant, if not exclusive clinical problem. Cirrhosis and portal hypertension with esophageal varices may ensue. Corticosteroids produce little if any benefit in such patients with late advanced disease and the addition of immunosuppresive agents has produced disappointing results.

Splenomegaly

This occurs in 20–30% of patients and is usually modest in degree. It alone does not serve as a definite indication for treatment, although it frequently accompanies active incapacitating disease requiring treatment. Massive enlargement may be observed, usually in association with significant hepatic disease. Prompt regression occurs in response to corticosteroids except where significant portal hypertension has developed. A picture of hypersplenism may occur and persist for many years without significant clinical problem. Rupture of the spleen does not seem to be a clinical hazard. Thrombocytopenic purpura, responding to steroid treatment, has been observed.

Cutaneous Disease

Sarcoidal skin lesions are of varied types and degree and are frequently present for many years but often without incapacitating disease. Localized erythematous infiltrative plaques associated with some hilar adenopathy may be the only manifestations of disease. This seems to occur particularly in white females. Local steroid creams are beneficial in such patients. Severely disfiguring cutaneous lesions may be a major feature and are often associated with significant mucosal changes. Chloroquine has been found to be effective in such extensive infiltrative disease, but its use is usually arbitrarily limited to a six-month course because of concern about irreversible retinal toxicity. A dose of 500 mg daily for the first two weeks followed by 250 mg daily for a six-month period may produce dramatic regression. The lesions often tend to recur after treatment is stopped, but the course of chloroquine treatment can be repeated at six month intervals. Repeat eye examinations are made, but no retinal changes have been observed with this regimen. After several courses of treatment, the disease may become inactive. Local steroid injections into cutaneous lesions may be effective but are usually impractical because of the wide distribution of lesions. Cutaneous lesions alone are usually not considered a sufficient indication for systemic corticosteroid treatment.

Mucous Membranes

Striking mucosal infiltrations frequently accompany significant skin sarcoid changes. Chronic nasal obstruction and sinusitis may represent major clinical problems and often respond to chloroquine treatment as outlined above. Submucous resections are usually to be avoided as septal perforations and ozena may result. Sinus surgery is occasionally necessary but much benefit can be achieved with antibiotics to clear secondary infection, local steroids or chloroquine, and saline lavage to the nose to minimize crusting. Endobronchial disease may produce bronchial narrowing with wheezing and atelectasis. Serious laryngeal involvement may result in hoarseness and stridor and necessitate prompt corticosteroid treatment.

Other Organ Involvement

Other manifestations requiring treatment include serious disease of the nervous system, especially meningeal disease and possible resultant internal hydrocephalus. Cranial and peripheral neuropathy may be present and evanescent with facial nerve palsies the most common. Cardiac involvement may result in various conduction defects and serious arrhythmias. Corticosteroids and anti-arrhythmic agents are used, but fatal arrhythmias still may occur. A picture of myocardopathy or even mitral valve prolapse and regurgitation has been encountered. Salivary and lacrimal gland involvement may produce a "sicca" syndrome. Muscle changes may result in significant weakness with some myalgias which respond promptly to corticosteroid treatment. Hypercalcemia or persistent hypercalciuria may require steroid treatment.

Complicating Infections

Concern about the possible development of tuberculosis in patients with already seriously diseased lungs has led some clinicians to advocate the use of isoniazid prophylaxis when corticosteroid treatment is initiated. Factors of tuberculin reactivity and the prevalent socioeconomic factors provide guidance, but the subsequent development of tuberculosis has been uncommon. Herpes zoster has been observed in several patients with sarcoidosis and may represent a feature of the disturbed immunologic system.

Summary

The course and prognosis of sarcoidosis is variable but appears to be favorably influenced by corticosteroid treatment when significant and potentially reversible involvement is identified. However, spontaneous remissions occur frequently when disease manifestations are mild. A period of observation of a few months often will clarify the need for treatment.

References

1. Longcope, W. T. and Frieman, D. G.: A Study of Sarcoidosis: Based on a Combined Investigation of 160 Cases Including 30 Autopsies from The Johns Hopkins Hospital and Massachusetts General Hospital, Medicine 31:1, 1952.
2. Mayock, R. L., Bertrand, P., Morrison, C. E., and Scott, J. H.: Manifestations of Sarcoidosis: Analysis of 145 Patients, with a Review of 9 Series Selected from the Literature, Am J Med 35:67, 1963.
3. Mitchell, D. N. and Scadding, J. G.: Sarcoidosis, Am Rev Resp Dis 110:774, 1974.
4. Siltzbach, L. E., James, D. G., Neville, E., Turiaf, J., Battesti, J. P., Sharma, O. P., Hosoda, Y., Mikami, R., and Odaka, M.: Course and Prognosis of Sarcoidosis around the World, Am J Med 57:847, 1974.

5. James, D. G., Neville, E., Siltzbach, L. E., Turiaf, J., Battesti, J. P., Sharma, O. P., Hosoda, Y., Mikami, R., Odaka, M., Villar, T. G., Djuric, B., Douglas, A. C., Middleton, W., Karlish, A., Blasi, A., Olivieri, D., and Press, P.: A Worldwide Review of Sarcoidosis, Ann NY Acad Sci 278:321, 1976.
6. Winterbauer, R. H., Belic, N., and Moores, K. D.: A Clinical Interpretation of Bilateral Hilar Adenopathy, Ann Int Med 78:65, 1973.
7. Koontz, C. H., Joyner, L. R., and Nelson, R. A.: Transbronchial Lung Biopsy Via the Fiberoptic Bronchoscope in Sarcoidosis, Ann Int Med 85:64, 1976.
8. Turiaf, J., Johns, C. J., Teirstein, A. S., Tsuji, S., and Wurm, K.: The Problem of the Treatment of Sarcoidosis: Report of the Subcommittee on Therapy, Ann NY Acad Sci 278:743, 1976.
9. Wurm, K., Rosner, R.: Prognosis of Chronic Sarcoidosis, Ann NY Acad Sci 278:732, 1976.
10. Johns, C. J., MacGregor, M. I., Zachary, J. B., and Ball, W. C. Jr.: Extended Experience in the Long-Term Corticosteroid Treatment of Pulmonary Sarcoidosis, Ann NY Acad Sci 278:722, 1976.
11. Young, R. C. J., Carr, C., Shelton, T. G., Mann, M., Ferrin, A., Laurey, J. R., and Harden, K.: *Sarcoidosis: Relationship between Changes in Lung Structure and Function*, Edited by J. Turiaf and J. Cabot. La Sarcoidose Rapp IV Conf Int Paris, Masson et Cie, 1967, pp. 455–464.

The Mount Sinai Journal of Medicine
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Primary Biliary Cirrhosis

SHEILA SHERLOCK

One of the fringe benefits of being a hepatologist married to a sarcoidologist is the chance to meet his friends. I have certainly benefited from and enjoyed my links with the world of Siltzbach. Louis has helped me in so many ways, as teacher, investigator, and particularly as visiting professor in the old Royal Free Hospital on the roof in the Gray's Inn Road and in the gorgeous new Royal Free Hospital in Hampstead. He has been not only lecturer but also cultural attaché for art and literature. It is an honor to contribute to this Festschrift and to wish Louis all happiness now and in the future.

I have chosen to write on primary biliary cirrhosis (PBC). This links our two fields of interest admirably. Primary biliary cirrhosis, chronic active hepatitis, and cryptogenic cirrhosis are the only three liver diseases in which circulating autoantibodies can be demonstrated in high titre and with some regularity. These include antibodies against nuclei (ANA), smooth muscle (SMA), and mitochondria (MA). There is considerable overlap among the three diseases. In PBC, the injury affects mainly intrahepatic bile ducts, whereas in chronic active hepatitis the emphasis is on liver cell destruction. Granulomas are found in the liver and elsewhere only in PBC. Therefore, in accord with Louis Siltzbach's interests, I will concentrate on this disease.

PBC is a form of chronic obstructive, nonsuppurative, granulomatous cholangitis. The advent of better diagnostic methods, particularly the serum mitochondrial antibody test, and the recognition of hepatic changes on needle liver biopsy sections has allowed earlier diagnosis, even when the patient is asymptomatic or presents with mild cholestasis. The number of cases being recognized all over the world is therefore increasing greatly. This chapter concerns the present position of PBC with respect to three aspects—immunologic changes, early diagnosis in the presymptomatic stage, and the current position of treatment.

Immunologic Aspects

PBC is a granulomatous disease. The liver shows lymphocytic accumulations, often in follicles, and many plasma cells. The granulomas may be histologically indistinguishable from those of sarcoidosis (Fig. 1). The granulomas are found not only in relation to damaged intrahepatic bile ducts but also can be found in lymph nodes outside the liver, in the hepatic hilum, in the omentum, and in the lungs. Such enlarged, fleshy glands in the porta hepatis in primary biliary cirrhosis are well recognized and may give rise to difficulties in diagnosis. Granulomas are particularly prominent in the early stages of the disease. Serial sections of a liver biopsy may be necessary to identify them.

Granulomas must be distinguished from sarcoidosis (Table I), although in general the picture is quite different (2). In particular, the Kveim-Siltzbach

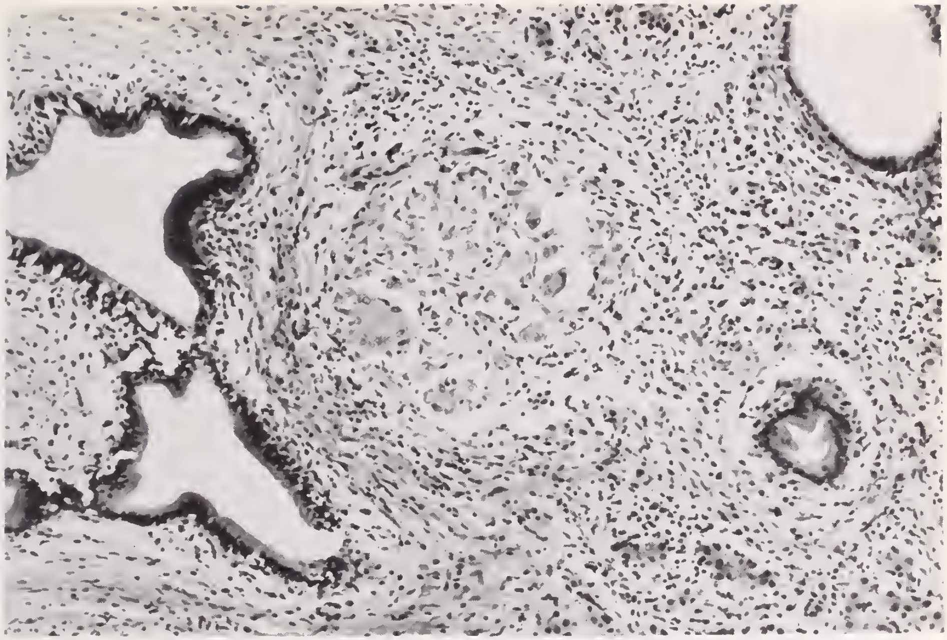

FIG. 1. Liver biopsy in a patient with primary biliary cirrhosis showing a granuloma adjoining an injured bile duct.

TABLE I

Sarcoidosis and Primary Biliary Cirrhosis Contrasted (after Stanley et al, 1972)

	Sarcoidosis	PBC
Sex	Equal	8:1 Female
Erythema nodosum	Yes	No
Uveitis	Yes	No
Pruritus	No	Yes
Xanthomas	No	Yes
Skin pigmentation	No	Yes
Steatorrhea	No	Yes
Bilateral hilar lymphadenopathy	Yes	No
Kveim test	Pos. (75%)	Neg.
Corticosteroids	Yes	No
Mitochondrial antibodies	No	Yes
Delayed-type hypersensitivity		
Depression	Yes	Yes
Prognosis	Good	Poor

reaction is negative in PBC. Certainly, granulomas in the liver per se in patients with sarcoidosis are not usually associated with significant cholestasis. Chronic intrahepatic cholestasis has however been reported in sarcoidosis particularly by Rudzki and coworkers (3) in young black men. The serum mitochondrial antibody test, however, was negative and the Kveim-Siltzbach test was not done. It remains uncertain whether or not these patients were in fact genuine cases of sarcoidosis.

Depression of delayed-type hypersensitivity can also be demonstrated by anergy to various skin test materials such as dinitrochlorobenzene (DNCB) and the Californian limpet. A significantly higher percentage of patients with PBC fail to react to tuberculin when compared with normal controls. There is impaired transformation of lymphocytes in relation to phytohemagglutinin. Finally, lymphocytes from patients with PBC are cytotoxic to human liver cells in tissue culture. The disturbed delayed type hypersensitivity reaction seems to be unrelated to raised levels of circulating autoantibodies. In particular, there is no correlation between disturbance of cell-based immunity and the serum mitochondrial antibody level or to the severity of the disease. The disturbance seems to be an effect rather than a cause.

There is a familial incidence of PBC. It has been reported in sisters, twins, and in mother and daughter (4). There is a significant increase in the incidence of mitochondrial antibodies in healthy relatives of patients with PBC. However, there seems to be no relationship between PBC and the histocompatibility antigens, blood groups ABO or rhesus (5).

Serologic abnormalities include an antibody against the inner membrane of mitochrondria in 83–98%. Although a very useful diagnostic test, it is negative in virtually all cases of extrahepatic biliary obstruction, and its significance is uncertain. It bears no relation to the clinical state of the patient or to the hepatic histologic stage.

Presymptomatic PBC

Among about 200 patients with PBC seen at the Royal Free Hospital, London between 1963 and 1975, 20 have been diagnosed before they have developed hepatobiliary symptoms such as pruritus (6). Eighteen were female, with a mean age of 47 years (range 23–62 years). The age is younger than in those who present when symptomatic, suggesting that the presymptomatic stage of PBC is passed through by many patients, but in only a minority is it discovered.

The diagnosis is often made when another disease is being considered, for instance, rheumatoid arthritis, keratoconjunctivitis sicca, or pernicious anemia. Primary biliary cirrhosis, like sarcoidosis, is a disease with multisystem involvement and it is not surprising that presymptomatic patients present with associated conditions. More patients with presymptomatic PBC might be diagnosed if such patients were screened by serum alkaline phosphatase levels, by serum IgM and by the mitochondrial antibody test.

Suggested clinical features include hepatomegaly and hepatosplenomegaly. Routine biochemical tests may reveal a raised serum alkaline phosphatase and this is an indication for estimating serum 5-nucleotidase and gamma glutamyl transpeptidase. Postprandial serum bile acid levels are a particularly sensitive indication of cholestasis. In some, simply a positive serum mitochondrial antibody raises suspicion of the diagnosis of PBC. Serum IgM is raised in about 80% and the level appears to stay uniformly high during the course, whereas the IgG tends to increase.

Liver biopsy features are particularly helpful. Diagnostic appearances are the finding of typical bile duct lesions, with damaged interlobular ducts surrounded by dense inflammatory infiltrate rich in plasma cells and histiocytes and with granuloma formation (7). Suggestive biopsy appearances are a lesion resembling chronic aggressive hepatitis, with scanty bile ducts, ductular proliferation, and loose lymphoid aggregates, even in the absence of classic bile duct lesions and granulomas. Using these criteria, suggestive or diagnostic liver biopsy was found in 75% of 20 patients with presymptomatic PBC (6). This is much higher than in unselected symptomatic cases. This can probably be explained by the earlier stage and younger age of the presymptomatic patients. Liver biopsy appearances become less specific as the lesion evolves. It is not possible to predict from an early stage on biopsy that the patient will have a long asymptomatic course. Presymptomatic PBC may remain histologically static for many years.

The course is variable. In the series of 20, 10 remained asymptomatic a mean of 4.5 years and even up to 10 years (Fig. 2). Symptomatic PBC runs a course of 6–7 years (range 4–14 years). Once symptoms develop, the course is similar to that of patients diagnosed at or after the onset of symptoms. It is impossible to predict which presymptomatic patients will become symptomatic and whether the course will be short or long.

Treatment

This is disappointing. Affected patients have both clinical and serologic evidence of an altered immune status. Corticosteroids, so often used with benefit in chronic active hepatitis (another disease associated with disturbed immunity), cannot be given to patients with primary biliary cirrhosis, be-

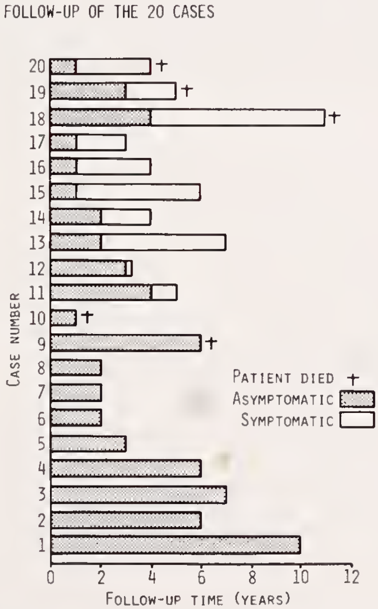

FIG. 2. Prognosis of 20 patients with primary biliary cirrhosis diagnosed at an asymptomatic stage, followed for many years or until symptomatic (Long, Scheuer, and Sherlock, 1976).

cause of the development of serious side-effects, particularly bone thinning. Azathioprine (Imuran®) treatment has been proposed. Between 1968 and 1974, azathioprine was used in a prospective controlled trial conducted at the Royal Free Hospital (8). Forty-five patients with symptomatic, but precirrhotic primary biliary cirrhosis, were admitted. Twenty-two of these received 2 mg/kg body weight azathioprine. During the first year, serum aspartate transaminase levels showed significant change in favor of the treated group, but improvement did not continue. Throughout the trial, serum alkaline phosphatase, bilirubin, cholesterol, albumin, and immunoglobulin M values showed no significant change. Titres of serum mitochondrial antibodies tended to become negative more often in the treated than the untreated. Pruritus cannot be assessed objectively, but seemed less in the treated than in the controls (Fig. 3). Serial hepatic biopsy specimens showed the development of cirrhosis equally in the two groups. Survival, as judged by the life table method was similar for the first 5 years of the trial (Fig. 4). There was, however, a significant difference in favor of the treated group in the sixth year, although the number of patients available for assessment at that time was extremely small. Treatment with azathioprine of patients with symptomatic but precirrhotic primary biliary cirrhosis does not seem to be dramatically beneficial. Whether patients at a presymptomatic stage might benefit more remains to be determined. There was some relief from pruritus, but no remarkable differences with respect to objective variables. Survival of those given azathioprine may be marginally longer than in those untreated, but the number available for long-term assessment was not sufficient to come to a definite conclusion.

D-penicillamine is an alternative therapy. In primary biliary cirrhosis, liver copper concentrations are increased, frequently into the range found in Wilson's Disease. This is due to prolonged failure of biliary copper excretion. The high liver copper concentration in Wilson's Disease is responsible for the

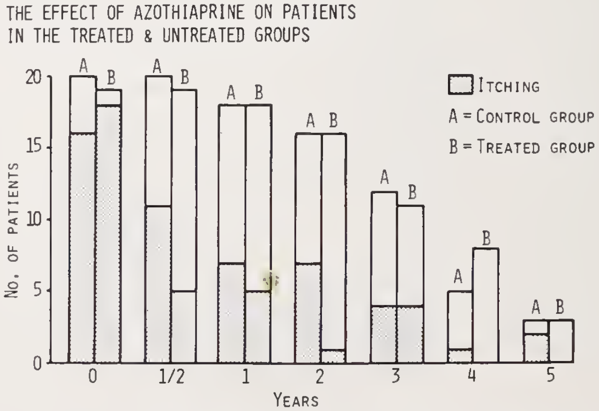

Fig. 3. Primary biliary cirrhosis. The effect of azathioprine in treated and control groups. For the first two years pruritus was less frequent in the treated group (Heathcote, Ross and Sherlock, 1976).

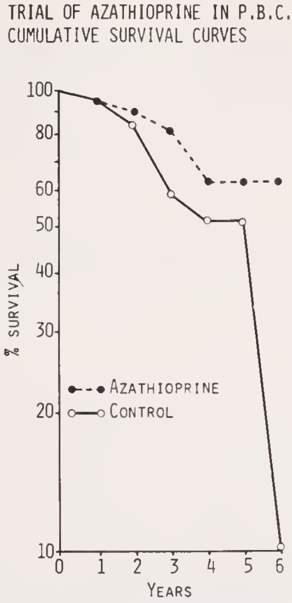

Fig. 4. Primary biliary cirrhosis. Cumulative survival curves show no significant difference between treated and control groups except at the 6th year when numbers in both are very small (Heathcote, Ross and Sherlock, 1976).

liver damage and ultimately for cirrhosis. Similarly, accumulation of hepatic copper in PBC may depress liver cell function and provoke collagen synthesis. D-penicillamine also may be beneficial because of its effect on collagen synthesis. It reduces the amount of collagen and the proportion of insoluble to soluble collagen in human skin and reduces the amount of connective tissue formed in experimentally induced rat cirrhosis. It is not known whether D-penicillamine will prevent the collagen deposition in PBC as the predominant type of cross-linking of this collagen has not been characterized. D-penicillamine is being used at the Royal Free Hospital in a randomized double-blind control trial in patients with primary biliary cirrhosis (9). After three months, patients taking 900 mg daily D-penicillamine showed a significant reduction in serum aspartate transaminase levels compared with a placebo group and this reduction appeared to be sustained. Serum bilirubin and alkaline phosphatase levels did not change significantly. In those having a second liver biopsy after one year in the trial, liver copper concentration had fallen by a significant degree in the treated compared with the placebo group. Histologically, improvement in cholestasis was seen in patients on the active drug, but the degree of inflammation and necrosis and the histologic stage remained similar in both groups. Thirty-two percent of the patients on D-penicillamine had to discontinue the drug because of side-effects, which included dyspepsia, taste impairment, skin rashes, and proteinuria. Because of the variable natural history of the disease and the observed longer survival because of earlier diagnosis, many years must elapse before it is known whether cirrhosis, portal hypertension and liver failure are delayed or prevented, and the survival prolonged. In the meantime, for an illness in which no other form of therapy appears to offer the prospect of halting or delaying progressive liver damage, treatment with D-penicillamine, preferably within controlled trials, is recommended despite the high incidence of toxicity. Lower dosages (500–600 mg daily) with aggressive corticosteroid cover to avoid toxic phenomena may result in a lower discontinuation rate through toxicity.

Symptomatic measures of proved value include oral calcium and medium chain triglyceride supplements, intramuscular fat-soluble Vitamins A, D and K, and Cholestyramine.

Summary

Primary Biliary Cirrhosis (PBC) is a disease where granulomas may be found in liver and elsewhere. It can be distinguished from sarcoidosis by the clinical and biochemical picture and the negative Kveim-Siltzbach test. Cell-mediated immunologic reactions are depressed. The serum mitochondrial antibody test is positive in about 90% and is of diagnostic value.

Primary biliary cirrhosis may be diagnosed at a presymptomatic stage by 1) recognition of commonly associated disease; 2) abnormal biochemical tests particularly increased serum alkaline phosphatase and immunoglobulin M levels; 3) presence of serum mitochondrial antibodies; and 4) diagnostic or compatible hepatic histology. The prognosis of the presymptomatic state is impossible but 2 to 10 years may pass before symptoms develop. The duration of the symptoms is 4 to 7 years.

A controlled prospective trial of azathioprine showed only doubtful benefit for the drug. Liver copper levels are very high in primary biliary cirrhosis and D-penicillamine (900 mg daily) reduces liver copper concentration and serum aspartate transaminase levels. This treatment may be beneficial, but side-effects are frequent.

Acknowledgments

It is a pleasure to thank my colleagues for the help they have given, in particular, Dr. J. Heathcote, Dr. S. Jain, Dr. R. Long, Dr. A. Ross, and Prof. P. J. Scheuer.

References

1. Sherlock, S.: Primary Biliary Cirrhosis. In *Diseases of the Liver and Biliary System*, 5th Edition, Lippincott, Philadelphia 1975, p. 285.
2. Stanley, N. N., Fox, R. A., Whimster, W. F., Sherlock, S., and James, D. G.: Primary Biliary Cirrhosis or Sarcoidosis—Or Both, N Engl J Med 287:1282, 1972.
3. Rudzki, C., Ishak, K. G., and Zimmerman, H. J.: Chronic Intrahepatic Cholestasis of Sarcoidosis, Amer J Med 59:373, 1975.
4. Tong, M. J., Nies, K. M., Reynolds, T. B., and Quismorio, F. P.: Immunological Studies in Familial Primary Biliary Cirrhosis, Gastroenterology 71:305, 1976.
5. Hamlyn, A. N., Morris, J. S., and Sherlock, S.: ABO Blood Groups Rhesus Negativity and Primary Biliary Cirrhosis, Gut 15:480, 1974.
6. Long, R. G., Scheuer, P. J., and Sherlock, S.: The Presentation and Course of Asymptomatic Primary Biliary Cirrhosis, Gastroenterology 72:1204, 1977.
7. Sherlock, S. and Scheuer, P. J.: The Presentation and Diagnosis of 100 Patients with

Primary Biliary Cirrhosis, N Engl J Med 289:674, 1973.

8. Heathcote, J., Ross, A., and Sherlock, S.: A Prospective Controlled Trial of Azathioprine in Primary Biliary Cirrhosis, Gastroenterology 70:656, 1976.
9. Jain, S., Scheuer, P. J., Samourian, S., McGee, J. O'D., and Sherlock, S.: A Controlled Trial of D-Penicillamine Therapy in Primary Biliary Cirrhosis, Lancet 1:831, 1977.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Hepatic Granulomata: Problems in Interpretation*

GERALD KLATSKIN

It is well known that granulomata can be found in the liver in a high proportion of patients with systemic granulomatous disease. It is not surprising, therefore, that liver biopsy has gained wide acceptance as a diagnostic tool in the investigation of such disorders as sarcoidosis and disseminated tuberculosis. However, the interpretation of hepatic granulomata is more difficult than is generally appreciated—first, because the etiology of such lesions can seldom be established on histologic grounds alone, and, second, because the presence of granulomata in the liver does not necessarily imply an underlying systemic granulomatous process. Indeed, unless these two points are borne in mind, the discovery of granulomata in the liver may prove to be misleading rather than diagnostic.

A brief review of our own experience with 742 cases of biopsy-documented hepatic granulomata will serve to illustrate some of the problems involved in their interpretation.

As shown in Table I, there were two major categories of lesions: epithelioid granulomata and lipogranulomata. The distinction between these two types of lesion was relatively simple and posed no problem. However, differentiation of epithelioid granulomata on histologic grounds alone was exceedingly difficult and often impossible. The 565 cases of epithelioid granulomata were encountered in three major groups of patients: 319 with granulomatous disease, 174 with underlying hepatic disease, and 72 with miscellaneous disorders that appeared to be neither primarily granulomatous nor primarily hepatic in nature.

As might be anticipated, such lesions were found in a high proportion of patients with underlying granulomatous disease, the incidence ranging from 47 to 100 percent. As shown in Table II, sarcoidosis, tuberculosis, and schistosomiasis were the principal disorders encountered in this group.

Of note is the inordinately high incidence of hepatic granulomata in sarcoidosis, 94 percent—a frequency considerably greater than that usually reported. We attribute this to the greater average length of our biopsy specimens, 27 mm, and our practice of examining serial sections. Assuming that the lesions are uniformly distributed, it can be estimated that a liver weighing 1500 grams would contain at least 15,000,000 granulomata if a single lesion was found in a 5 micron section of a 30 mg biopsy specimen. Since the average number of granulomata found in our biopsy sections was 5, it would appear that the liver in sarcoidosis usually contains about 75,000,000 granulomata. Surprisingly, such lesions gave rise to few clinical manifestations or hepatic functional impairment. As shown in Table III, only a minority of patients exhibited hepatosplenomegaly and abnormalities in serum

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* Presented at the West Japan Liver Meeting, Kurume, October 22, 1976.

TABLE I

Hepatic Granulomata Demonstrated by Biopsy in 5500 Patients (6075 Biopsies)

Epithelioid granulomata	565/5500 (10%)
Granulomatous disease	319/433 (74%)
Hepatic disease	174/4724 (4%)
No other hepatic or granulomatous disease	72/343 (21%)
Lipogranulomata	177/5500 (3%)

TABLE II

Hepatic Granulomata Demonstrated by Biopsy in 433 Patients with Documented Granulomatous Disease

Sarcoidosis	217/231	(94%)
Tuberculosis	70/164	(43%)
Schistosomiasis	19/25	(76%)
Brucellosis	4/4	(100%)
Berylliosis	4/4	(100%)
Temporal (granulomatous) arteritis	2/2	(100%)
Visceral larva migrans	1/1	(100%)
Eosinophilic granuloma of lung	1/1	(100%)
Starch granuloma of peritoneum	1/1	(100%)
Total	319/433	(74%)

TABLE III

Clinical Features Suggestive of Liver Disease in 231 Patients with Sarcoidosis

	Hepatic Granulomata Demonstrated	No Hepatic Granulomata on Biopsy
Hepatomegaly	33/217 (15%)	3/14 (21%)
Splenomegaly	45/217 (21%)	2/14 (14%)
Jaundice	5/217 (2%)	0/14 (0%)
Ascites	3/217 (1%)	0/14 (0%)
Spider hevi	3/217 (1%)	0/14 (0%)
Hyperbilirubinemia	8/217 (4%)	0/14 (0%)
BSP retention	37/70 (53%)	2/16 (13%)
Alkaline phosphatasemia	32/217 (15%)	2/14 (14%)
Increased SGOT	28/176 (16%)	0/11 (0%)
Serum albumin, < 3.5 g/dl	37/215 (17%)	1/14 (7%)
Serum albumin, < 3.0 g/dl	23/215 (11%)	1/14 (7%)
Serum globulin, > 4.0 g/dl	66/215 (31%)	2/14 (14%)
Serum γ globulin, > 1.5 g/dl	10/37 (27%)	0/1 (0%)

bilirubin, alkaline phosphatase, transaminase and serum proteins. However, half those tested exhibited mild BSP retention.

Of interest, granulomata were encountered in the liver not only in disseminated tuberculosis, but also in localized forms of the disease, that, at least clinically, appeared to involve only one or two tissues (Table IV), an observation previously emphasized by Haex and van Beek (1).

The hepatic lesions in most forms of granulomatous disease were remarkably similar, so that identification of their etiology was seldom possible on histologic grounds alone. As a rule, the diagnosis depended on the clinical features and the results of serologic tests, bacterial and viral cultures, and skin tests. The exceptions in which the hepatic granulomata exhibited distinctive features included the presence of acid-fast bacilli in tuberculosis, ova in schistosomiasis, larvae and eosinophils in visceral larva migrans, granulomata in the walls of arterioles in granulomatous arteritis, and characteristic birefringent granules in starch granuloma.

Illustrated in Figure 1 is the classic lesion of sarcoidosis, a sharply circumscribed compact mass of epithelioid and giant cells, with little inflammation and no necrosis. However, many sarcoidal lesions are atypical in showing a

TABLE IV

Hepatic Granulomata Demonstrated by Biopsy in 164 Patients with Tuberculosis

Pulmonary	23/93	(25%)
Active	20/64	(31%)
Arrested	3/29	(10%)
Pulmonary and other tissues	10/14	(71%)
Pleural effusion	3/7	(43%)
Lymph nodes	6/9	(67%)
Alone	4/7	(57%)
With other tissues	2/2	(100%)
"Primary" hepatic	6/6	(100%)
Meningeal	1/9	(11%)
Other tissues	4/8	(50%)
Single	1/5	(20%)
Multiple	3/3	(100%)
Disseminated (miliary)	17/18	(94%)
Total	70/164	(43%)

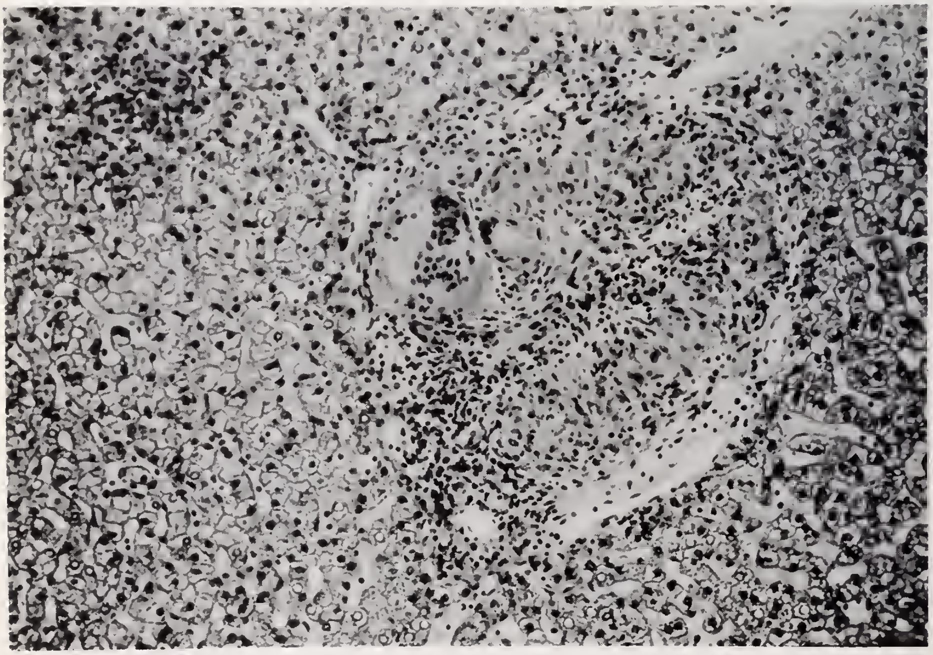

FIG. 1. Classic granuloma in sarcoidosis.

diffuse inflammatory reaction. Although such lesions never show caseation, they often exhibit foci of fibrinoid necrosis.

Shown in Figure 2 is the typical caseating hepatic granuloma found in a patient with tuberculosis. However, such lesions are rare. More commonly, the hepatic lesions in tuberculosis resemble those found in sarcoidosis. In such lesions, the etiology may be established by the demonstration of acid-fast bacilli (Fig. 3). Unfortunately, as shown in Table V, acid-fast bacilli were demonstrable in only 10 percent of our tuberculous granulomata, so that usually identification of their etiology depended on recovery of tubercle bacilli in cultures of sputum, body fluids, or other tissues.

Illustrated in Figure 4 is a large necrotic granuloma suggestive of a tuberculous lesion. However, it was attributable to brucellosis, as proved by blood culture.

The granuloma shown in Figure 5 was found in a patient with hilar adenopathy and pulmonary infiltrates. Both the biopsy and radiographic findings were thought to be consistent with sarcoidosis. However, a careful occupational history and a positive beryllium patch test established that the patient had berylliosis.

Of hepatic granolomata that can be identified on histologic grounds alone, schistosomiasis is a prime example, since the lesions almost invariably contain characteristic ova (Fig. 6).

However, serial sectioning may be required to demonstrate such ova, illustrating the importance of this technique.

Another example of a granuloma that could be identified on histologic

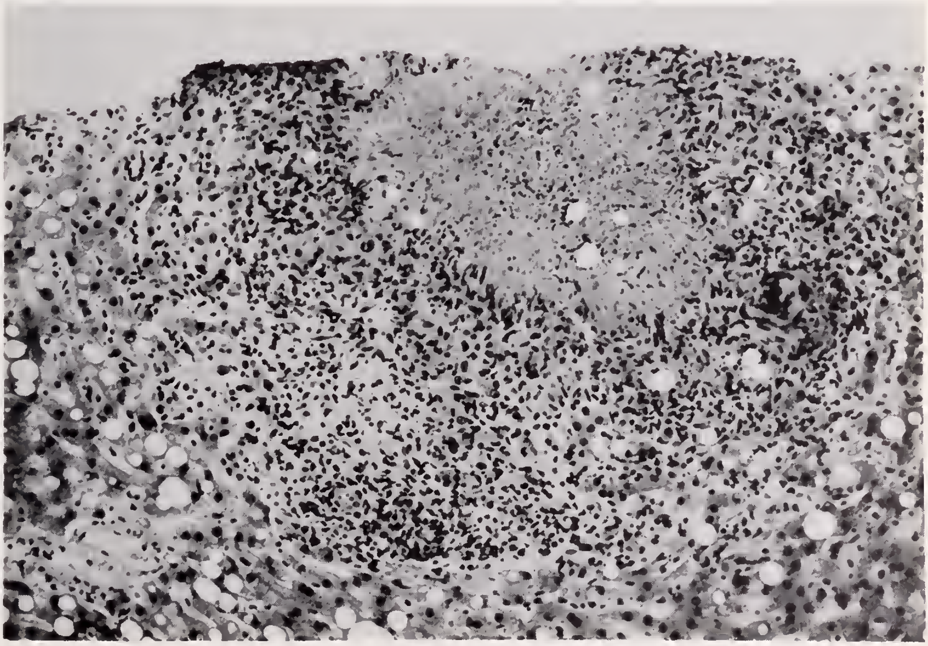

FIG. 2. Caseating granuloma in tuberculosis.

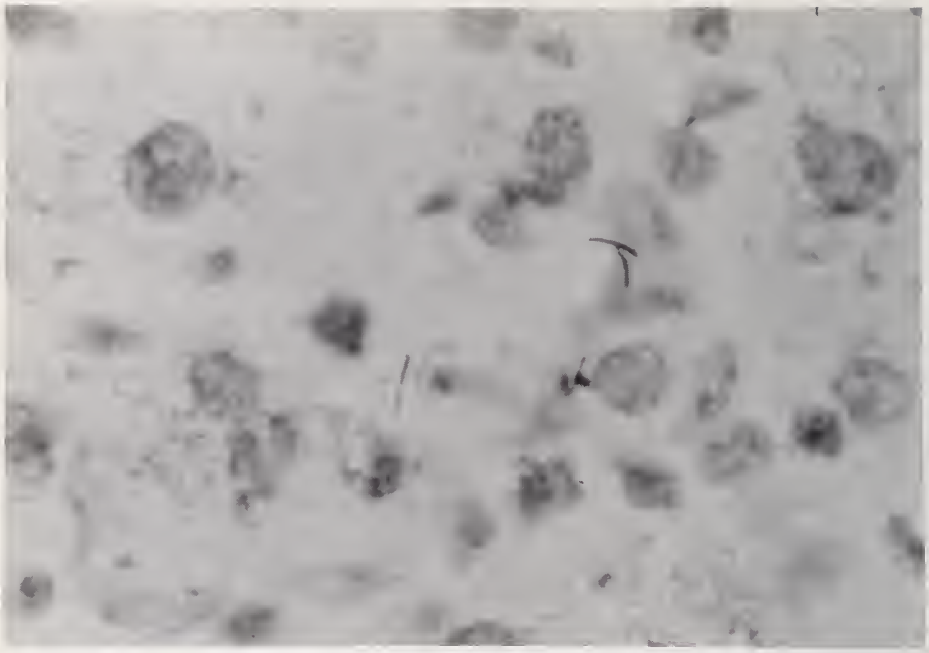

FIG. 3. Acid-fast bacilli in sarcoid-like granuloma.

TABLE V

Incidence of Acid-Fast Bacilli in Hepatic Granulomata Presumably Tuberculous in Nature

Pulmonary Tbc	0/33
Miliary Tbc	3/18 (17%)
"Primary" hepatic Tbc	3/5 (60%)
Tuberculous adenitis	1/6 (17%)
Other forms of Tbc	0/8
Total	7/70 (10%)

grounds alone is illustrated in Figure 7. This lesion was encountered in an elderly woman with prolonged unexplained fever. As can be seen, the granulomatous reaction was in the wall of an arteriole, suggesting the diagnosis of granulomatous arteritis, which was confirmed by biopsy of a temporal artery.

Occasionally, polarization microscopy is required to identify the etiology of hepatic granulomata. The liver biopsy section illustrated in Figure 8 shows a large hyalinized granuloma. It was encountered in a young woman who had undergone exploratory laparotomy on several occasions for unexplained abdominal pain. On the last two occasions multiple granulomata were found in the liver, peritoneum, and retroperitoneal tissues. Attempts to establish the etiology, including a therapeutic trial with antituberculous therapy, proved fruitless. However, polarization microscopy revealed the presence within the granulomata of numerous birefringent granules with Maltese crosses, the typical features of starch granules. The granulomata were of iatrogenic origin

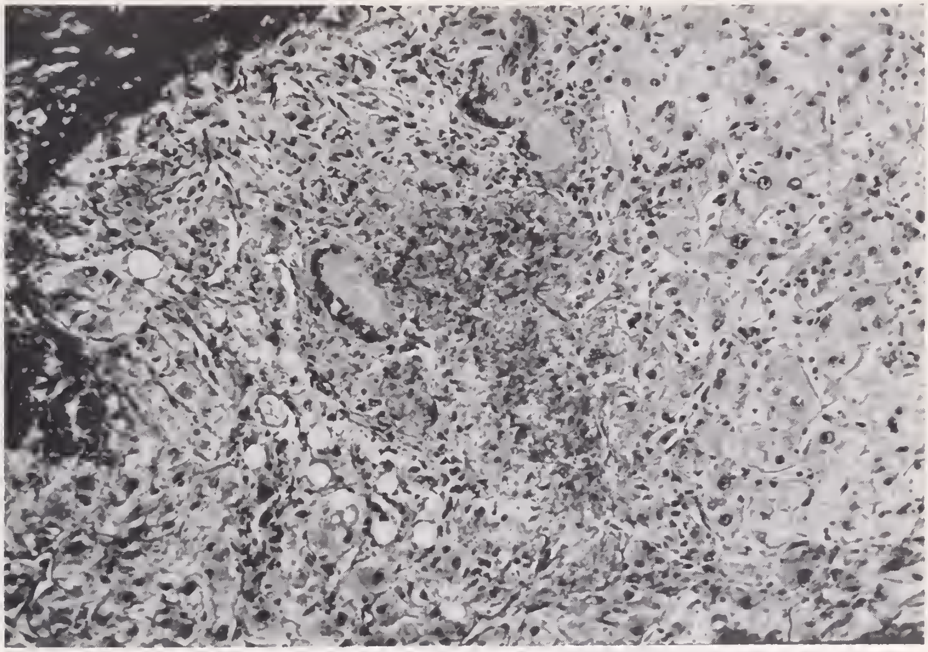

FIG. 4. Large necrotic granuloma in brucellosis.

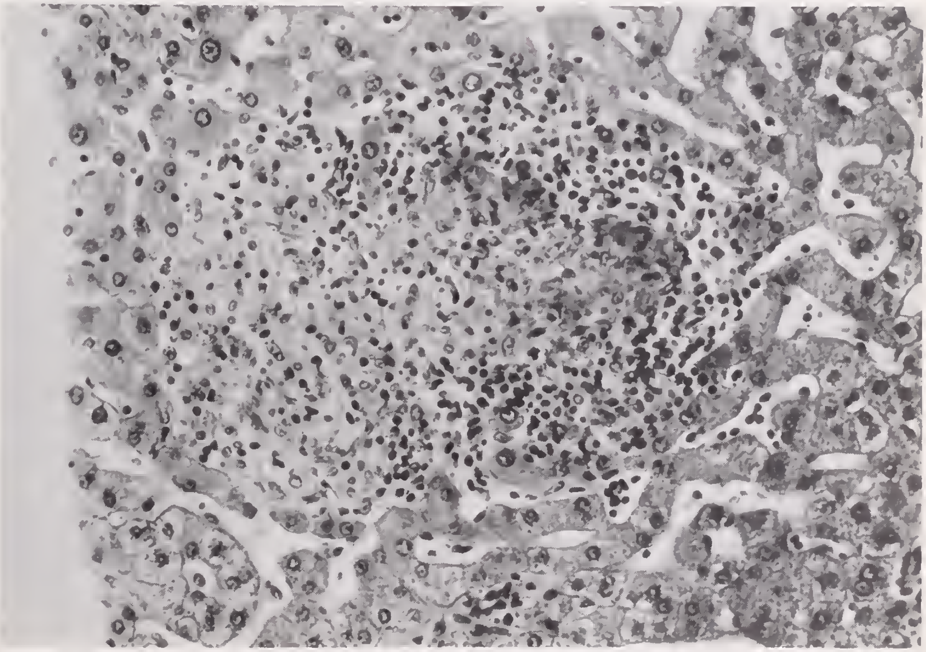

FIG. 5. Sarcoid-like granuloma in berylliosis.

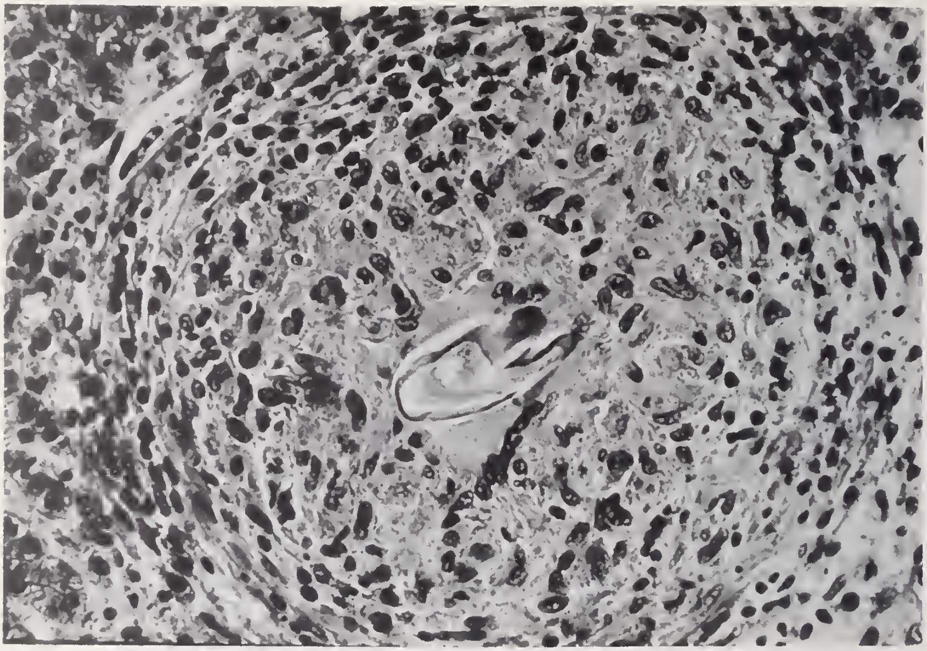

FIG. 6. Epithelioid granuloma in schistosomiasis with ovum.

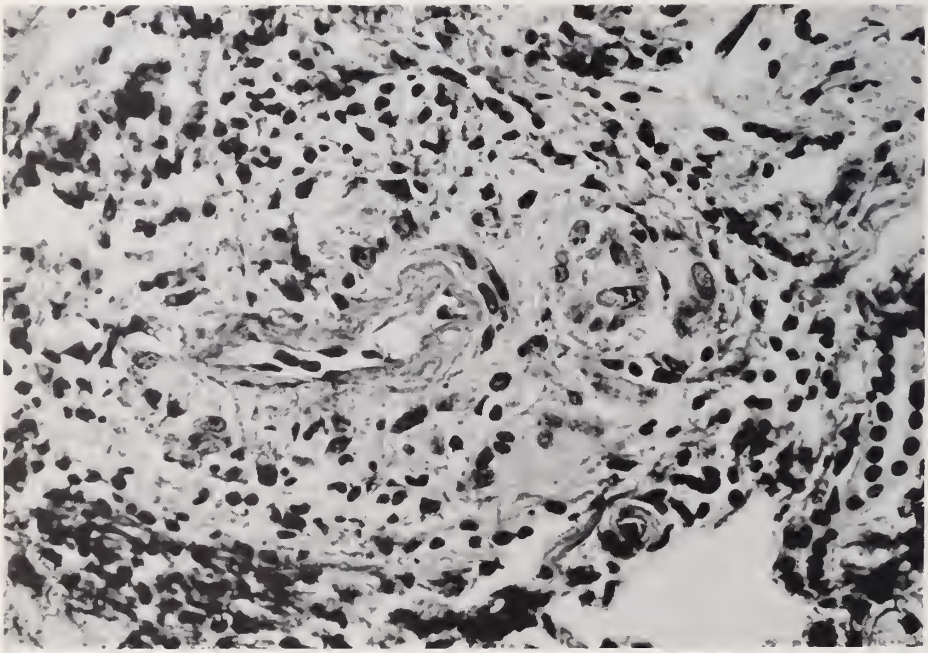

FIG. 7. Granulomatous reaction in the wall of a hepatic arteriole in a patient with giant-cell (temporal) arteritis.

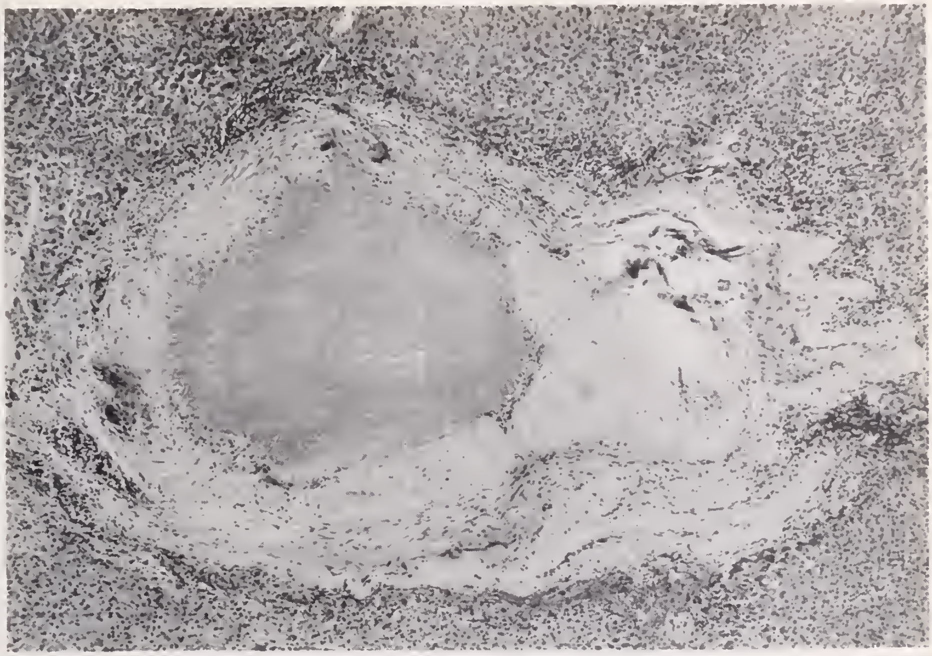

FIG. 8. Large hyalinized starch granuloma deep in liver.

and related to the multiple laparotomies the patient had undergone. Moreover, it was apparent that they were not responsible for the patient's major complaint of abdominal pain. This led to further investigation which revealed the presence of a ureteral stone that had not been recognized previously.

As indicated in my introduction, hepatic granulomata occur not only in systemic granulomatous disease, but also as a nonspecific lesion in patients with a wide variety of acute and chronic hepatic disorders. As shown in Table VI, this occurs most frequently in primary biliary cirrhosis.

Usually, in primary biliary cirrhosis, the granulomata lie adjacent to or around degenerating ducts (Fig. 9) and are accompanied by the other histologic features of that disease, so that they pose no diagnostic problem. However, occasionally the granulomata are located in the midzone or around a central vein, as in Figure 10, in which case the question of systemic granulomatous disease invariably arises. The problem is further complicated by the fact that the lymph nodes in the porta hepatis in primary biliary cirrhosis often contain granulomata that are indistinguishable from those of sarcoidosis.

The occurrence of nonspecific granulomata is not limited to primary biliary cirrhosis. Indeed, they may be found in any acute or chronic liver disease; we have found them in Laennec's cirrhosis, acute viral hepatitis, and cytomegalovirus hepatitis.

Although most granulomata found in patients with underlying liver disease prove to be nonspecific, the possibility of coexistent granulomatous disease must always be ruled out.

TABLE VI

Hepatic Granulomata Demonstrated in 4724 Patients with Biopsy-Documented Liver Disease

Cirrhosis	110/1199	(9%)
Laennec's	36/659	(5%)
Postnecrotic	6/205	(3%)
Primary biliary	59/148	(40%)
Others	9/187	(5%)
Hepatitis, acute	31/975	(3%)
Viral	13/632	(2%)
Toxic and drug-induced	13/191	(7%)
Infectious mononucleosis	3/20	(15%)
Cytomegalovirus mononucleosis	2/2	(100%)
Others	0/130	(0%)
Hepatitis, chronic active	4/34	(12%)
Biliary and pancreatic disease	17/484	(4%)
Biliary obstruction	8/325	(2%)
Acute and chronic pericholangitis	9/159	(6%)
Malignancy	2/427	(<1%)
Lymphoma	1/65	(2%)
Primary and metastatic	1/362	(<11%)
Fatty infiltration	8/393	(2%)
Other hepatic lesions	2/1212	(<1%)
Total	174/4724	(4%)

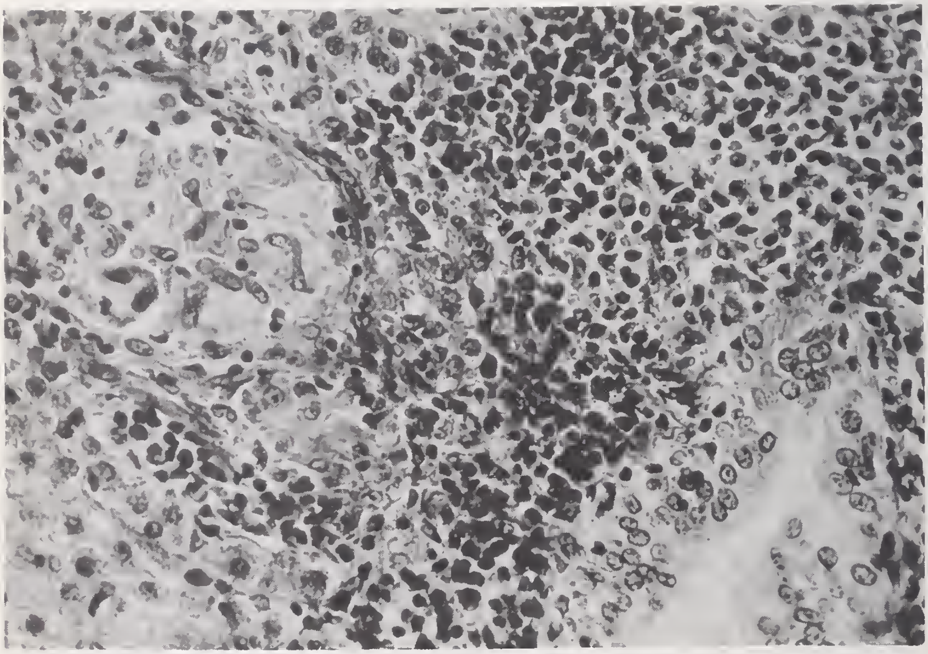

FIG. 9. Portal granuloma in primary biliary cirrhosis. Granuloma lies close to a degenerating interlobular duct seen in the lower right corner of the field.

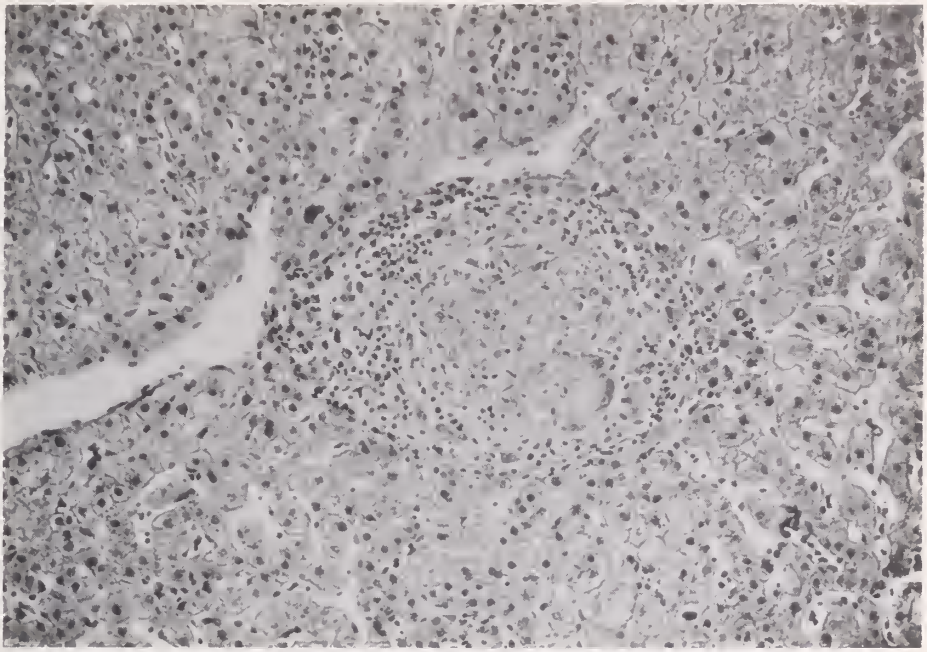

FIG. 10. Centrally located sarcoid-like granuloma in primary biliary cirrhosis.

We noted a large granuloma found in a patient with severe $\mathrm{HB_sAg}$-positive viral hepatitis. On first assessment this was interpreted as a nonspecific granuloma. However, further investigation revealed bilateral hilar adenopathy and a strongly positive Kveim reaction indicating that she had sarcoidosis in addition to viral hepatitis.

Another point that must be borne in mind is that both sarcoidosis and brucellosis occasionally produce extensive granulomatous destruction of the liver leading to the development of cirrhosis.

Figure 11 illustrates an example of sarcoidal cirrhosis in a black woman with documented advanced pulmonary sarcoidosis. In the course of her disease, serial biopsies revealed progressive destruction of the liver by granulomata leading ultimately to the cirrhosis seen in this section. In this case, the granulomata were still evident. However, the granulomata may give rise to cirrhosis and then disappear. This is illustrated in Figure 12 which shows the cirrhosis found on followup biopsy in the patient with granulomatous hepatitis due to brucellosis previously presented (Fig. 4). Obviously, therefore, when granulomata are found in a cirrhotic liver, the remote possibility of underlying granulomatous disease must be excluded.

The third category of patients who exhibited granulomata were those whose underlying disease appeared to be neither primarily granulomatous nor primarily hepatic in nature (Table VII). Of the 72 patients in this group, 19 had intraabdominal disease, such as lymphoma, carcinoma, ulcerative colitis, or Crohn's disease; 8 had documented acute viral or bacterial infec-

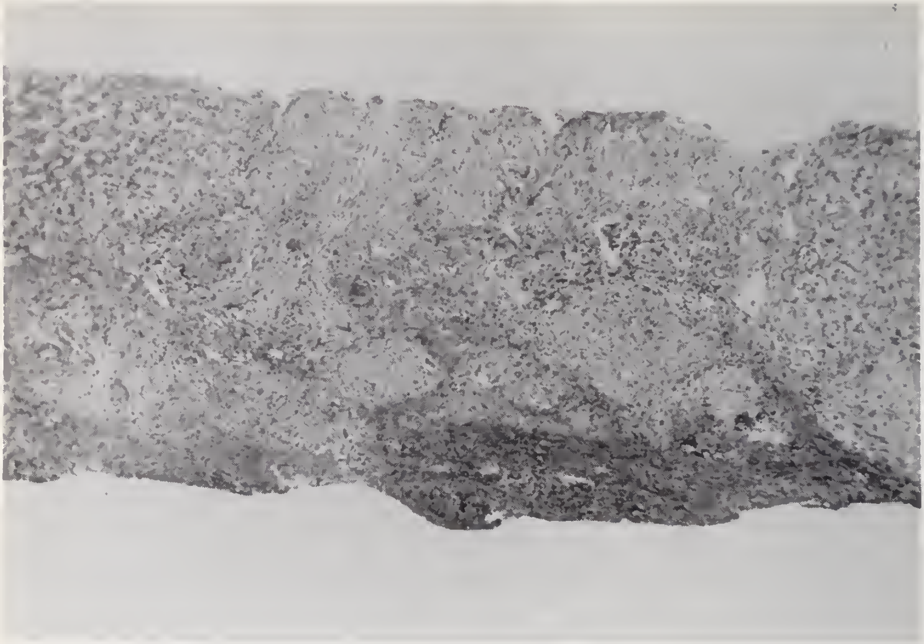

FIG. 11. Sarcoidal cirrhosis showing numerous granulomata within fibrotic septa.

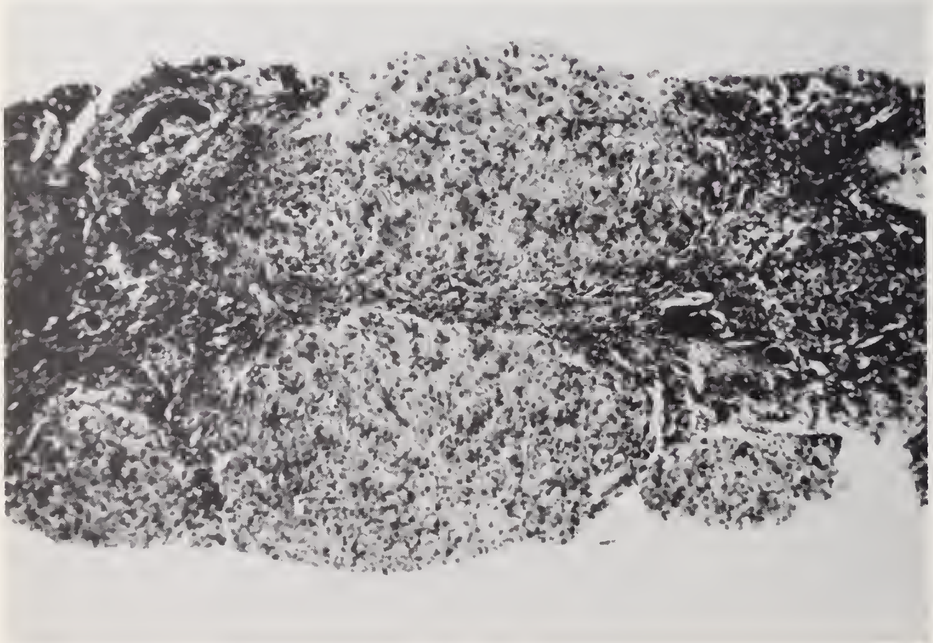

FIG. 12. Cirrhosis following recovery from acute brucellosis and the necrotizing granulomatous hepatitis illustrated in Figure 4.

TABLE VII

Hepatic Granulomata Demonstrated by Biopsy in 343 Patients with no Evidence of Other Hepatic or Granulomatous Disease

Intra-abdominal disease	19
Lymphoma	10
Carcinoma	5
Ulcerative colitis	2
Crohn's disease	2
Infection	8
Viral	4
Bacterial	4
Psoriasis and hyperuricemia (± gout) (3 additional cases with frank sarcoidosis)	8
Diagnosis not established	37
Fever of unknown origin	17
Others	20
Total	72/343 (21%)

tions; 8 had psoriasis accompanied by gout and/or hyperuricemia; and 37 had disorders that defied diagnosis despite exhaustive investigation. Of interest, 17 of the latter had prolonged unexplained fever. Although it is highly probable that some of the hepatic granulomata in this group, especially in patients with intraabdominal malignancy and ulcerative bowel disease, represented nonspecific responses to their underlying disease, it is conceivable that others, particularly those associated with prolonged fever, were attributable to specific infectious agents that had escaped detection by the diagnostic methods we employed. The lesions in this group were indistinguishable from those of sarcoidosis and tuberculosis.

Figure 13 illustrates the sarcoid-like granuloma in a patient with fever and splenomegaly due to Hodgkin's disease, but who had no evidence of lymphomatous infiltration of the liver. Similar nonspecific granulomata are seen in psoriasis and gout and in patients with unexplained fever and hepatosplenomegaly.

Although none of the patients with nonspecific granulomata found in association with hepatic or other diseases exhibited the usual features of sarcoidosis, the possibility had to be considered that they had an unusual form of the disease limited to the liver. However, as shown in Table VIII, the results of Kveim tests failed to provide any supporting evidence for this. Thus, with one exception, none of the patients in this group reacted to Kveim antigen. The fact that positive Kveim reactions were obtained in 69% of the 109 patients with sarcoidosis and in none of the 73 controls, including 37 with tuberculosis and 36 with nongranulomatous hepatic disease, attests to the specificity and sensitivity of the Chase-Siltzbach antigen employed in these studies. The one unexpected positive Kveim reaction occurred in a tuberculin-negative patient with psoriasis, hyperuricemia and hepatic granulomata, who had no pulmonary lesions, hilar adenopathy or other features of sarcoi-

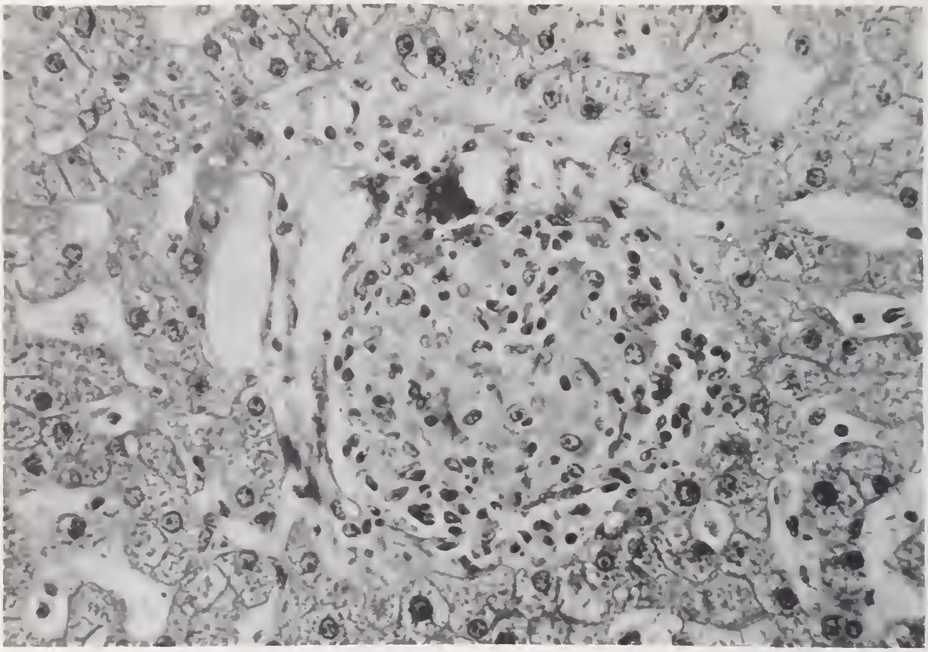

FIG. 13. Nonspecific sarcoid-like granuloma in a patient with Hodgkin's disease involving the lung and spleen but with no evidence of lymphomatous infiltration of the liver.

TABLE VIII

Results of Kveim Tests (Positive reactions/number of tests)

Granulomatous disease	
Sarcoidosis	75/109 (69%)
With hepatic granulomata	58/87 (68%)
No hepatic granulomata	6/10 (60%)
No liver biopsy	10/12 (83%)
Tuberculosis	0/37 (0%)
With hepatic granulomata	0/5
No liver biopsy	0/32
Brucellosis	
With hepatic granulomata	0/1 (0%)
Eosinophilic granuloma of lung	
With hepatic granulomata	0/1 (0%)
Hepatic granulomata in liver disease	0/29 (0%)
Hepatic granulomata in nonhepatic nongranulomatous disease (1 positive in psoriasis)	1/20 (5%)
Hepatic disease with no granulomata	0/36 (0%)
Summary	
Sarcoidosis	75/109 (69%)
Other diseases	1/124 (<1%)

dosis. Conceivably, the psoriasis in this case was associated with sarcoidosis involving the liver alone or in combination with other tissues that produced no clinical manifestations. The possible relationship between psoriasis and sarcoidosis has been discussed in two previous reports (2, 3) and is of interest, since we have encountered 3 other patients with psoriasis, gout, and/or hyperuricemia who exhibited the classic features of sarcoidosis.

The possibility that at least some of the nonspecific granulomata under discussion represent quiescent tuberculous lesions cannot be excluded with certainty. The somewhat higher incidence of positive tuberculin reactions in this group as compared to patients with sarcoidosis lends some support to this possibility (Table IX).

In addition to epithelioid granulomata, the type of lesion we have been discussing thus far, the liver not infrequently contains lipogranulomata. As shown in Table I, we have encountered such lesions in 3 percent of our patients subjected to biopsy.

Lipogranulomata have distinctive morphologic features that distinguish them from epithelioid granulomata, so that they rarely pose a diagnostic problem unless the pathologist is unfamiliar with their appearance. Characteristically, as shown in Figure 14, the lesion consists of a sharply circumscribed mass of vacuolated histiocytes interspersed with scattered lympho-

TABLE IX

Positive Tuberculin Reactions in Sarcoidosis and in Patients with Hepatic Granulomata but no Other Evidence of Hepatic or Granulomatous Disease

	PPD #1	PPD Int.	PPD #2	Total
Sarcoidosis	[illegible]	11	20	31/231 (13%)
Nonspecific hepatic granulomata	7	5	11	23/72 (32%)

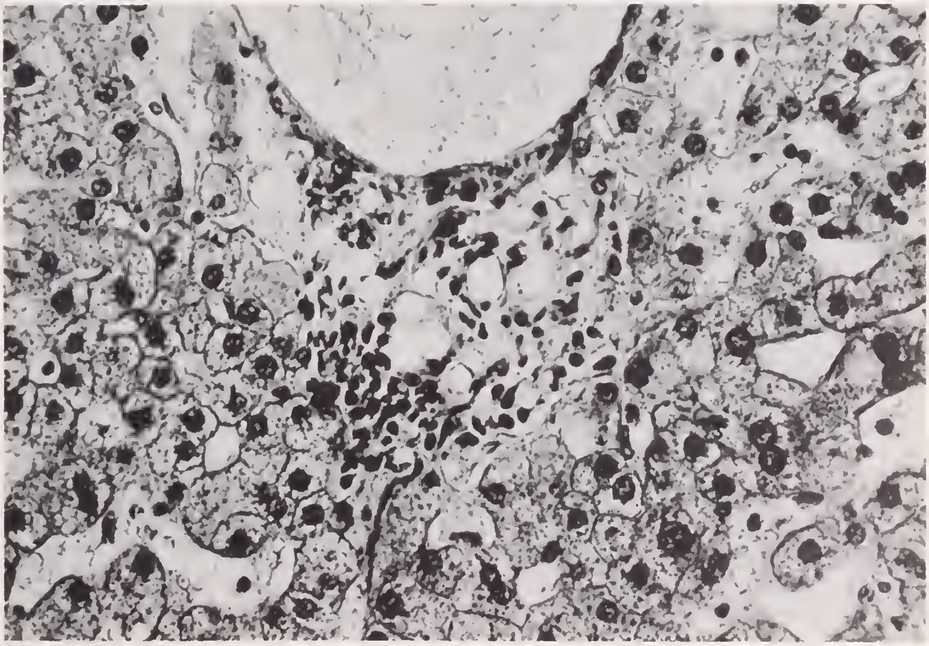

FIG. 14. Lipogranuloma attached to a central vein.

cytes and a few strands of collagen. Most lipogranulomata, as in this case, are attached to the walls of central veins. Occasionally, however, they may be found in portal triads.

Boitnott and Margolis[4] have presented convincing evidence that lipogranulomata represent a reaction to absorbed mineral oil. Although it is not generally appreciated, a remarkably large volume of mineral oil is consumed by all individuals, at least in the United States, as a result of its widespread use in food processing. Our own studies indicate that such lesions may persist for years, but never progress and have no clinical or diagnostic significance.

Summary

Granulomata occur in the liver not only in patients with systemic granulomatous disease, but also in a variable number with underlying liver disease, and in a heterogeneous group of disorders that appear to be neither primarily hepatic nor primarily granulomatous in nature.

The hepatic granulomata found in association with liver disease are only rarely attributable to coexistent systemic granulomatous disease, and probably represent a nonspecific response to the underlying liver disease.

In the heterogeneous group of diseases that appear to be neither primarily hepatic, nor primarily granulomatous in nature, hepatic granulomata may represent a nonspecific response in some instances, such as intraabdominal malignancy and ulcerative bowel disease, but, in others, particularly those with unexplained prolonged fever, may be attributable to specific agents that are overlooked or escape detection by currently available diagnostic measures.

The etiology of hepatic granulomata can seldom be established on histologic grounds alone, and usually requires collateral clinical and laboratory evidence for identification.

In a minority of cases, hepatic granulomata show diagnostic histologic features. However, even in such cases, special stains, serial sections, and polarization microscopy may be required for identification.

References

1. Haex, A. J. Ch. and Van Beek, C.: *Tuberculosis and Aspiration Liver Biopsy: Its Clinical Significance in Diagnosis and Therapy*. Haarlem, De Erven F Bohn N V, 1955.
2. Kaplan, H. and Klatskin, G.: Sarcoidosis, Psoriasis, and Gout: Syndrome or Coincidence? Yale J Biol Med 32:335, 1960.
3. Bunim, J., Kimberg, D. V., Thomas, L. B., van Scott, E. J., and Klatskin, G.: The Syndrome of Sarcoidosis, Psoriasis, and Gout, Ann Intern Med 57:1018, 1962.
4. Boitnott, J. K. and Margolis, S.: Mineral Oil in Human Tissues. II. Oil Droplets in Lymph Nodes of the Porta Hepatis, Bull Johns Hopkins Hosp 118:414, 1966.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Adverse Drug Reactions Involving the Liver: Probable Mechanisms

FENTON SCHAFFNER AND HANS POPPER

Hepatic drug reactions are conventionally separated into predictable and nonpredictable ones (1). The former are dose-dependent, have usually a short latent period, and can be reproduced in animals. A direct toxic action of the drug or its metabolite is incriminated and this results in steatosis or hepatocellular necrosis, as is the case with some antineoplastic drugs, such as mithramycin, or mitomycin C, or therapeutic agents taken in excess such as acetaminophen (paracetamol). Some drugs such as methotrexate may induce a time and dose-dependent fibrosis or even cirrhosis. Jaundice is caused by liver cell injury, cholestasis, or hemolysis. A few drugs like the tetracyclines interfere with synthetic or secretory processes, especially lipoprotein formation and release. This leads to steatosis with hepatic failure. Steatosis without necessarily impaired function may also occur following drug use. Alcohol is the most common example and several metabolic processes are involved.

Nonpredictable drug reactions occur only in a few of the persons exposed; they have no or a hazy dose dependency and a prolonged latent period, are rare in children, and are not or only exceptionally produced in experimental animals. They are a problem in drug application since the adverse reactions, sometimes fatal, may be detected only after widespread clinical use, as in the case of some muscle relaxants, antidiabetic and antihypertensive drugs (1). The causal relation is difficult to prove and is so far not even uniformly accepted as in the case of halothane (2). Originally the reactions were considered to be an idiosyncracy without defining the term, but now they are regarded as hypersensitivity, suggesting an allergic component. As more reactions were observed, they were classified into cholestatic and hepatitic, with only few causing noninflammatory necrosis or steatosis, and then usually on a circulatory basis. Cholestasis not associated with hepatitis is either the result of a primary interference with the function of the bile secretory apparatus of the hepatocytes or an injury of the intrahepatic bile ductular and ductal system. The hypersensitivity in all these instances is the result of an unusual metabolic reaction and may be genetically explained, with an immunopathic reaction a possibility. The similarity of the hepatitis with viral hepatitis suggests immune aggression induced by the drug although an abnormal or unusual metabolic transformation of the drug remains a possibility. Unusual immune reactions and metabolism are linked, because a metabolite formed in higher concentration or persisting longer because of unusual genetic (3) or environmental (4) circumstances may induce the immunopathic reaction.

The purpose of this paper is to discuss the interplay of aspects of both metabolism and immune responsiveness which is necessary to produce adverse reactions in the liver. Since the cell membrane is the target of the immunologic reaction and its components are also potentially changed both by predictable and nonpredictable reactions, its drug-induced lesions will be referred to first.

Plasma Membrane Changes

The plasma membrane is a lipid bilayer with a liquid hydrophobic central portion while the external and internal surfaces consist of hydrophilic ionic portions of the phospholipids (5). Protein molecules scattered throughout the bilayer are necessary to maintain the membrane (integral membrane proteins). They have hydrophobic portions held in the lipid center of the membrane bilayer and hydrophilic portions which protrude both above the membrane surface or into the cytoplasm or in both directions. Carbohydrate moieties attached to the hydrophilic portion of the integral membrane proteins protruding above the cell surface serve as specific receptors binding hormones, antibodies, neurotransmitters, and other substances that enter the cell or otherwise influence the interior of the cell. The distribution of the protein molecules in the membrane varies depending on the physical contacts of the cell, on substances that bind to their receptor sites and on cytoplasmic skeletal elements. The last are rigid microtubules which anchor proteins or contractile microfilaments which move them about in the membrane. Drugs influence the cytoskeletal structure associated with the membrane and its control in many ways. For instance, some substances cause aggregation of integral membrane proteins to form small clusters or larger caps which can then enter the cell by endocytosis. This aggregation can be prevented by drugs which nonspecifically injure cellular function but it also can be prevented by drugs like colchicine or vinblastine which depolymerize the microtubular protein tubulin or like cytochalasin B which disrupts microfilaments. Some drugs enhance membrane protein aggregation like the tertiary amine anesthetics. Probably many drugs or their metabolites influence the cytoskeletal structure by directly affecting microtubules and microfilaments or by nonspecifically interfering with cellular function. Furthermore, interactions of drugs may alter the cell membrane in complex ways so that membrane proteins are internalized or shed. The latter can expose hitherto "unseen" portions of the membrane proteins to the immune system of the body thereby stimulating an immune response. Thus drugs taken up and metabolized by hepatocytes not only alter the internal composition of these cells but also their surfaces. The alteration in the surface membrane can affect cellular function on one hand and the recognition of the membrane proteins by the immune system on the other. As yet unknown factors govern the rates of synthesis, polymerization, and orientation of the cytoskeletal proteins, tubulin of microtubules, and actin and myosin of microfilaments.

Lymphoid Response to Altered Plasma Membranes and Drug Hepatitis

The exposure of shed normal integral membrane proteins or the more easily detached nonessential peripheral membrane proteins or those altered by binding with drug metabolites may induce humoral antibody formation as well as a cell-mediated immune response. The nature and intensity of both types of immune responses depend on the rate of release of the surface proteins, on their binding to macrophage or lymphocyte surfaces, on their antigenicity and on the reactivity of the host immune system. Drugs or their metabolites may influence several steps in this complex process by influencing the rate at which protein is made available to act as an antigen, the phagocytic ability of macrophages and their lysosomal digestive function, the surface binding of lymphocytes, the rate of antibody formation and the rate of production of specifically cloned lymphocytes and finally the availability of receptor sites on the hepatocellular surface for immune reactions. Drugs may even compete with their metabolites or even have opposite effects in some of these processes. Hepatocellular injury may play an adjuvant role by enhancing immune responsiveness on one hand and a suppressing role on the other by slowing drug metabolism or reducing available receptor sites. The hepatocellular injury also stimulates collagen production and deposition. The pericellular fibrosis interferes with blood-liver exchange of nutrients and oxygen but it may also be protective by keeping antibody molecules and killer lymphocytes away from the hepatocellular surface. The mechanisms described whereby an altered plasma membrane becomes the target of an immunologic attack have been more clearly elucidated in hepatitis B virus infections (6). Many similarities in clinical, biochemical, and pathologic features in viral and drug induced hepatitis support the hypothesis of membrane alteration as the key to drug-induced disease.

The immunologic attack initiated by drugs and eventually causing hepatocellular injury may develop rapidly within two weeks after drug exposure or may be delayed and appear slowly after months of therapy. Halothane hepatitis is an example of the first type and the chronic hepatitis from isoniazid, oxyphenisatin, methyldopa, or even aspirin, is an example of the latter group.

Drug Metabolism and Liver Injury

When a drug is given by mouth it is carried to the liver by the portal circulation bound to serum proteins, most often albumin. The transfer across the hepatocellular plasma membrane probably occurs with the help of polysaccharide binding sites on the external surface attached to integral membrane proteins of the hepatocytes. Whether the drug is internalized by endocytosis, or by change in the shape or position of the membrane protein, or by dissolution in the lipid bilayer of the membrane is unknown. Once inside the cell a nonpolar drug, preferentially lipid soluble, is usually bound to a heme containing cytoplasmic cytochrome in the smooth endoplasmic reticulum (7). At least two and perhaps many such cytochromes are present. The one which metabolizes mainly aliphatic compounds is called cytochrome P-450 because its maximal light absorption in carbon monoxide atmosphere is at 450 nanometers and is the basis of most hydroxylation and demethylation. The one which metabolizes mainly aromatic compounds is P-448 or P_1450 and is exemplified by aryl hydrocarbon hydroxylase reactions. Each of these cytochromes in the drug metabolizing enzyme system can be induced by appropriate drugs or chemicals. Some drugs and particularly environmental chemicals such as polychlorinated biphenyls (PCB) induce more than one type of cytochrome. In the endoplasmic reticulum the drug is oxidized or deacylated to the form that is active pharmacologically and then it is further oxidized. It becomes more polar and may be conjugated most often with glucuronide or especially if in excess with glutathione for urinary or biliary secretion (8). Occasionally the drug moves to the soluble fraction of the cytoplasm where sulfatation or acetylation can occur.

Intermediary Metabolites as Biologically Active (Toxic or Carcinogenic) Agents

The initial metabolic step involves oxidation at one carbon atom with formation of an oxidized intermediary and water with the help of molecular oxygen, hence the name "mixed function oxidase" applied to the drug metabolizing enzyme system. Various intermediaries form in this initial stage of oxidation, some are free radicals, others are dihydroxylated. For instance, methyldopa is converted to a superoxide, acetaminophen to an epoxide and possibly a dihydroxy compound and carbon tetrachloride and possibly halothane to a free radical. Further metabolism in one or more steps, which varies with the drug, may involve such enzymes as epoxide hydrase. As a result, a more stable and polar intermediate is formed which is then often conjugated with a very polar compound. This makes the original drug, which was usually nonpolar, still more polar and readily excreted into the urine or bile depending upon its molecular weight.

When more intermediary is formed than can be handled by the normal pathway, it sometimes escapes, only to be scavenged by secondary pathways. These may involve combining with vitamin E to remove free radicals or with glutathione to remove epoxides. The latter combinations are further metabolized to form mercaptides which are also secreted in bile or urine. The rate of degradation of escaped intermediaries depends on many endogenous or exogenous factors. Examples of the former are hormonal balance, the activity of the epoxide hydrase, the availability of substrate for conjugation, and the amount of glutathione or pantothenic acid available for scavenging. The latter factors include diet (particularly protein content), intake of other drugs, and environmental factors (pesticides and PCB in fat tissue) (4). Excesses of a drug, such as after suicidal-acetaminophen-overdosage, may deplete glutatione so that epoxide escapes the scavenging mechanism and injures organelles. Furthermore, other cellular glutatione-dependent pathways may be impaired. Drugs and environmental agents may compete for conjugation and hence lessen removal of more reactive intermediaries.

The drug reaction depends on availability, the amount and life span of the active agent, either the original drug, an intermediary or, rarely, a terminal metabolite. Usually it becomes injurious by binding to cell macromolecules like protein, RNA or DNA (7). Some of the macromolecules are structural components, some are enzymes, and some are informational in nature. Each drug or metabolite seems to bind preferentially to certain types of macromolecules and probably at specific sites.

While covalent binding to protein has been considered the cause of hepatocellular necrosis, recent evidence does not prove this to be a necessary consequence; the complex may represent a neoantigen that elicits an immunologic reaction. Binding to DNA initiates carcinogenesis if the involved complex is not removed by DNA repair enzymes.

A few drugs and other chemicals, including environmental ones, are toxic and inactivated by the transformation system. With most, the metabolite is toxic. A few intermediaries may injure the vascular endothelium leading to veno-occlusive disease or the Budd-Chiari syndrome. Urethane is an example of the former and oral contraceptives of the latter. Vinyl chloride monomer probably induces angiosarcoma via a similar pathway.

The injurious metabolic effect is thus nonpredictable because life span and amount of the active metabolites depend on the kinetics of the forming and degrading enzymes regulated by many genetic and environmental factors discussed above which in addition are antagonistic or synergistic.

Cholestasis

A single mechanism cannot explain drug induced cholestasis and many drugs have several effects (9). Some drugs or their metabolites probably directly interfere with bile secretion by precipitating with bile acids in the pericanalicular zone. Chlorpromazine, or its metabolites, is an example of such a drug, but it has also other effects and this may explain why it produces jaundice in only a few cases. Other drugs, notably contraceptive and anabolic steroids, probably interfere with bile acid secretion by blocking micelle formation. They are deposited in the canalicular membrane, compete for the biliary anion excretory pathway or inhibit the Na^+K^+-ATPase-dependent ion pump responsible for bile acid independent bile flow. The latter effect is shared with chlorpromazine metabolites.

Possibly the rate at which the final metabolic product is delivered to the bile secretory apparatus determines the degree of interference with bile acid excretion. Still other drugs injure the hepatocyte severely enough so that all functions including that of bile excretion are impaired. Drugs and hormones may influence the cytoskeleton including the one attached to the canalicular membrane sufficiently to produce cholestasis. Alteration of the plasma membranes by drugs or metabolites may thus lead to development of hepatitis on one side and to cholestasis on the other with one reaction, both reactions or neither requiring interposition of an immune ("allergic") response by the host.

Complexities in the Production of Adverse Reactions

Opposing forces are active at each step of drug uptake, metabolism and disposition of metabolites as well as at each step of formation of neoantigens and response of the body to these proteins (Fig. 1). Genetic factors play a

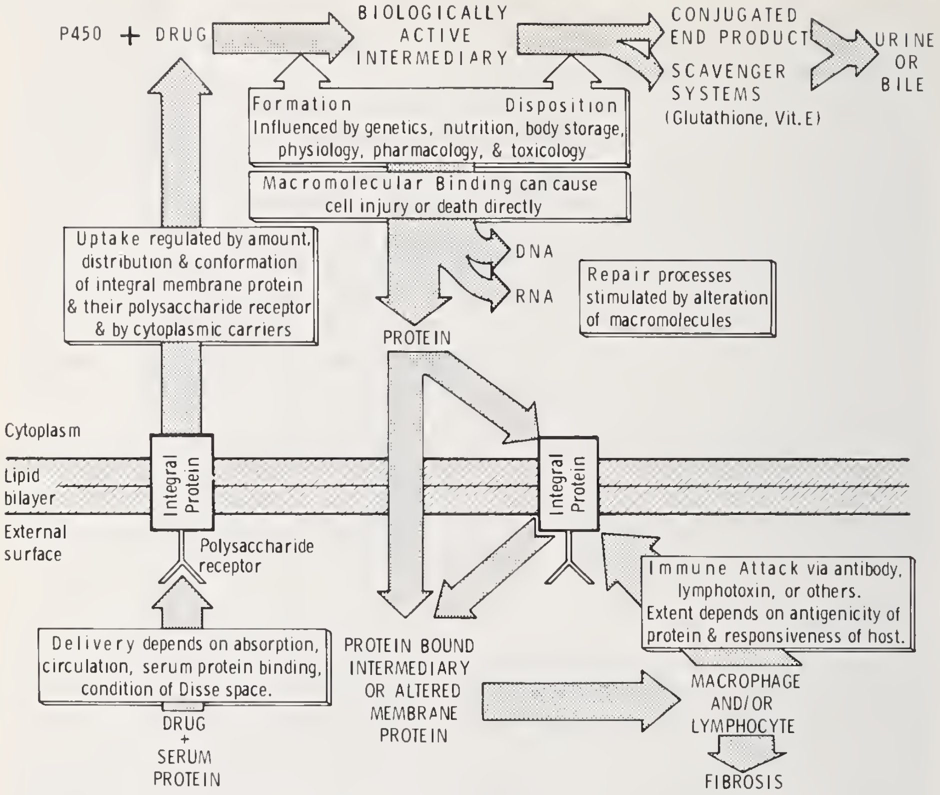
P450 + DRUG
BIOLOGICALLY ACTIVE INTERMEDIARY
CONJUGATED END PRODUCT
SCAVENGER SYSTEMS (Glutathione, Vit. E)
URINE OR BILE
Formation
Disposition
Influenced by genetics, nutrition, body storage, physiology, pharmacology, & toxicology
Macromolecular Binding can cause cell injury or death directly
DNA
RNA
PROTEIN
Repair processes stimulated by alteration of macromolecules
Uptake regulated by amount, distribution & conformation of integral membrane protein & their polysaccharide receptor & by cytoplasmic carriers
Cytoplasm
Lipid bilayer
External surface
Integral Protein
Integral Protein
Polysaccharide receptor
Immune Attack via antibody, lymphotoxin, or others. Extent depends on antigenicity of protein & responsiveness of host.
Delivery depends on absorption, circulation, serum protein binding, condition of Disse space.
DRUG + SERUM PROTEIN
PROTEIN BOUND INTERMEDIARY OR ALTERED MEMBRANE PROTEIN
MACROPHAGE AND/OR LYMPHOCYTE
FIBROSIS

FIG. 1. Scheme illustrating some of the complex factors in drug metabolism and disposition active in leading to adverse reactions affecting the liver.

major role in all of these steps but except for slow and fast metabolizers of some drugs, such as slow and fast isoniazid acetylators, and for congenital defects in immune responsiveness, little is known about genetic control. The rate of the initial step in metabolism can be accelerated by induction of the responsible enzymes by environmental pollutants, other drugs or even the drug in question. Liver cell injury reduces the rate of drug metabolism as does any viral infection which induces interferon. Indeed all natural or synthetic interferon inducers drastically reduce the rate of drug metabolism by decreasing the activity of cytochrome P-450 (10). The rate is also decreased by protein malnutrition and by competition from endogenous or the same exogenous factors just mentioned. Similarly, the rate of disposition of the reactive intermediary metabolite via the normal detoxification pathways can be accelerated by induction and slowed by competition. The rate of repair of macromolecules altered by drug metabolite binding varies under different physiologic and pharmacologic circumstances. The binding sites on the cell macromolecules may also be competitively blocked by other substances or they may be altered by changes in macromolecular conformation because the cytoskeleton is altered by drugs or cellular injury.

The accepted classification of adverse hepatic reactions is thus confirmed by newer pharmacologic and immunologic observation.

Predictable toxicity including also steatosis and vascular injury results from action usually of an intermediary metabolite on a specific organelle.

Nonpredictable reactions are, as a rule:

a. Hepatitic, since they are mediated through an immune mechanism directed against the plasma membrane altered by the drug or its metabolites (direct, i.e., nonimmunologic hepatitic reactions are rare). Hepatitis may develop rapidly within two weeks or slowly only after months of exposure. Both forms probably require metabolic transformation, plasma membrane alteration and immune response but the reason for differences in the time of onset are unknown.

b. Cholestatic, resulting from direct interference with bile excretion by the drug or from alteration of the mechanisms that control bile flow. A role of immune reactions in this condition has not been defined.

The three main types of reactions may be combined in variable proportions in individual cases and the same drugs may elicit different mechanisms. One or another reaction, however, predominates with each drug and during different time periods in the same case. Cholestasis particularly may persist after all else has subsided.

Conclusion

For a drug to produce cellular injury, it or its metabolites must wend their way through a devious biochemical pathway filled with detours and obstacles as well as rapid slides. A drug reaction, whether a predictable toxic effect or nonpredictable hepatitis or cholestasis, may result from a direct action of the drug or its metabolite on a specific cell structure, or may be allergic, that is the result of an immune reaction initiated in some fashion by the drug or its metabolites. Only with the direct toxins are the pathways simple enough to quantitate so that dose relations can be established. With most drugs that cause adverse reactions, predictability itself is not yet possible. Dose relations probably do exist in individual cases but these are lost in the myriad of other steps, some of which amplify and others diminish the effect of the drug in question. The multiplicity of effects at each step also makes prevention of adverse drug reactions in the liver a distant goal.

References

1. Perez, V., Schaffner, F., and Popper, H.: Hepatic Drug Reactions. In *Progress in Liver Diseases, Vol. 4*. Edited by H. Popper and F. Schaffner. Grune and Stratton, New York 1972, p. 597.
2. Walton, B., Simpson, B. R., Strunin, L., Doniach, D., Perrin, J., and Appleyard, A. J.: Unexplained Hepatitis following Halothane, Br Med J 1:1171, 1976.
3. Kalow, W. and Inaba, T.: Genetic Factors in Hepatic Drug Oxidations. In *Progress in Liver Diseases, Vol. 5*. Edited by H. Popper and F. Schaffner. Grune and Stratton, New York 1976, p. 246.
4. Gillette, J. R.: Environmental Factors in Drug Metabolism, Fed Proc 35:1142, 1976.
5. Nicolson, G. L. and Poste, G.: The Cancer Cell: Dynamic Aspects and Modifications in Cell-Surface Organization, N Engl J Med 295:197–203, 253, 1976.
6. Gudat, F., Bianchi, L., Sonnabend, W., Thiel, G., Aenishaenslin, W., and Stalder, G. A.: Pattern of Core and Surface Expression in Liver Tissue Reflects State of Specific Immune Response in Hepatitis B, Lab Invest 32:1, 1975.

7. Mitchell, J. R., Nelson, S. D., Thorgeirsson, S. S., McMurtry, R. J., and Dybing, E.: Metabolic Activation: Biochemical Basis for Many Drug-Induced Liver Injuries. In *Progress in Liver Diseases, Vol. 5*. Edited by H. Popper and F. Schaffner. Grune and Stratton, New York 1976, p. 259.
8. McLean, A. E. M. and Day, P. A.: The Effect of Diet on the Toxicity of Paracetamol and the Safety of Paracetamol-Methionine Mixtures, Biochem Pharmacol 25:37, 1975.
9. Popper, H., Schaffner, F. and Denk, H.: Molecular Pathology of Cholestasis. In *The Hepatobiliary System: Fundamental and Pathological Mechanisms*. Edited by W. Taylor. Plenum, New York 1976, p. 605–629.
10. Renton, K. W. and Mannering, G. J.: Depression of the Hepatic Cytochrome P-450 Mono-Oxygenase System by Administered Tilorone {2,7-bis[2-(diethylamino)ethoxyl]fluoren-9-one dihydrochloride}, Drug Metab Dispos 4:223, 1976.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Alpha-1-Antitrypsin and Disease

ROBERT A. NORUM, ALEXANDER G. BEARN, WILLIAM A. BRISCOE, AND ANNE BRISCOE

The capacity of serum to inhibit the proteolytic activity of trypsin was discovered in the early part of the century. Clinical interest in the major trypsin inhibitor of serum, alpha-1-antitrypsin (AAT) did not develop until 1964 when deficiency of this globulin was related to familial emphysema (1). Since then severe deficiency of AAT has also been shown to produce neonatal hepatitis and juvenile cirrhosis. Severe deficiency of AAT, partial deficiency, or electrophoretic variation of AAT continue to be related to a growing list of disease states.

Alpha-1-antitrypsin is a glycoprotein of molecular weight 50,000 and is so named for the alpha-1-globulin position it occupies in the standard serum protein electrophoresis. Electrophoresis of serum in starch at an acid pH has demonstrated more than 20 AATs of different electrophoretic mobilities (2). Family studies showed that the electrophoretic mobility of AAT is determined by codominant genes. The electrophoretic phenotype is now called the protease inhibitor type, or Pi type, and variants have been assigned letters of the alphabet in the order of the electrophoretic mobility (e.g., Z is the slowest). In most populations, 85% of individuals or more have the Pi M. These sera contain about 2.2 mg/ml AAT as measured by immunodiffusion. AAT quantity can also be measured by the capacity of the serum to inhibit the activity of trypsin on a chromogenic substrate. A few of the heterozygous and homozygous Pi types are associated with reduced quantities of AAT in serum.

Genetically determined severe deficiency with serum quantities of 0.8 mg/ml or less has been found thus far only in the Pi types ZZ, SZ, – (pronounced "null"), S-, and Z- with the first two the most common. The null gene produced no detectable AAT. The presence of the heterozygous state for this gene can only be detected by the study of Pi types and AAT quantity in family members. All of the other genes have been detected by differences in the electrophoretic mobility or isoelectric pH of the AATs they produce. Serum from a person heterozygous for these genes (excluding Pi-) shows the presence of two different AATs, representing the codominant expression of the genes in the Pi type.

The variations in the electrophoretic mobility of AATs produced by different genes were at first thought to be due to differences in sialic acid content, but the electrophoretic variations persisted after removal of sialic acid. An alternative hypothesis is that the mobility variations are due to differences in the amino acid sequence. Such amino acid substitutions have been found in type Z (3) and type S (4). Among patients with severe AAT deficiency and

RAN is supported in part by a research grant from the National Institutes of Health # HL/GM 18876.

emphysema Pi ZZ is the most frequent, occurring with a frequency of about 1 per 5,000 births, with wide variability between ethnic groups.

Thus far only severe deficiency of AAT and its associated Pi types have been clearly related to disease states. In people with normal levels of AAT and in those who are heterozygous for one of the genes for AAT deficiency, the serum quantity of AAT can be induced to rise by a number of stimuli such as pregnancy, estrogens, corticosteroids, and typhoid vaccination. In persons with severe deficiency these stimuli do not increase the serum level significantly. Carriers of one deficiency allele cannot be reliably distinguished from persons who are homozygous for the normal AAT allele by quantitation of AAT alone since the levels in these two groups overlap.

The genes for AAT quantity and electrophoretic mobility as determined by Pi type are located on the autosomes. Since in most families a patient with very low AAT levels has parents with only partial deficiency the inheritance of severe deficiency and associated diseases shows an autosomal recessive mode of transmission.

Familial emphysema

Patients with severe deficiency of AAT develop an emphysema that differs from emphysema of other etiologies in that it usually begins earlier in life. Although a few children with severe deficiency of AAT and emphysema have been described, most patients develop the condition near the end of the third decade.

Figure 1 shows the prevalence of emphysema in Pi Z subjects in relation to age. The fall in prevalence after age 50 may be due to deaths in the group with emphysema. Although about 80% of PiZ subjects get emphysema it is also clear that some individuals with severe deficiency of AAT escape clinical

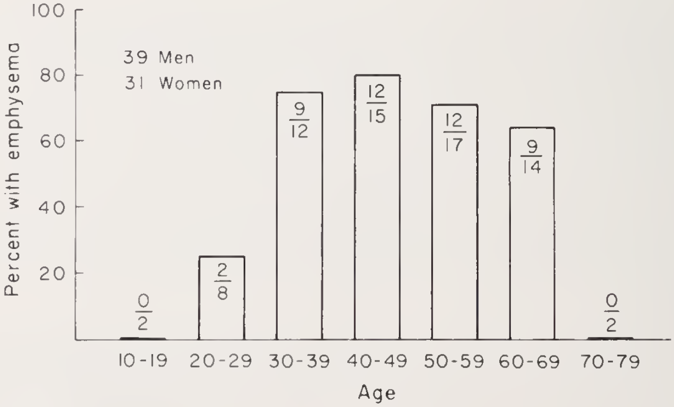

FIG. 1. Emphysema in alpha-1 antitrypsin deficiency. Data plotted from reference 2, Figure 7. Seventy people with Pi Z were ascertained from a population survey, relatives of subjects with Pi Z, and routine serum protein electrophoresis on hospitalized patients. Although the mean ages of men and women were the same, emphysema was more prevalent in the man (.05 > p > .01). Possible differences in the smoking habits between the two groups were not given. The fraction in each bar represents the number of subjects with emphysema divided by the number of subjects in that age group.

manifestations of emphysema even past the age of 60. Thus other factors, either environmental or genetic, must be making an important contribution to the development of emphysema. One candidate for a contributing influence is the level of elastase in leucocyte granules. Some correlation between high elastase activity in the presence of low AAT activity with emphysema of an especially early onset and great severity has been suggested (5). Such a correlation supports the current hypotheses regarding the pathogenesis of emphysema and AAT deficiency which propose that the principle function of AAT in the lung, which fails in severely deficiency patients, is the inhibition of the leucocyte or macrophage proteases (6). The majority of people with severe deficiency of AAT develop emphysema but severe deficiency accounts for only a relatively small percentage of patients with chronic obstructive pulmonary disease (COPD). While the lung disease in most patients with severe deficiency is emphysema in some the clinical picture of bronchitis predominates.

Cigarette smoking is probably a special hazard to patients with severe deficiency of AAT. In one series of patients with severe deficiency and signs of chronic obstructive pulmonary disease the mean age of onset of dyspnea was age 44 among those patients who had never smoked (7). Among the cigarette smokers the mean age of onset of dyspnea was a decade earlier. Chronic bronchitis occurred in 60% of the smokers, a prevalence twice that found in the nonsmoking group. Infection probably accelerates the course of the pulmonary changes. In a few patients symptoms began with or were aggravated by episodes of pneumonia. One sixth of patients report recurrent bronchitis.

The chest x-ray shows a decrease in peripheral vasculature which is most prominent in the lower lung fields, a pattern also seen in emphysema of other etiologies. The ventilatory clearance of radio-active xenon is also more delayed in the lower lung fields. Even in the absence of smoking the pulmonary changes are slowly progressive. In one series one half the deaths from respiratory failure occurred between the ages of 40–49 with a few deaths in the preceding decade. At the same time patients with chronic obstructive pulmonary disease and severe deficiency of AAT have been observed in their 70's emphasizing the extreme range of variability in this manifestation of severe deficiency.

There is a still unsolved controversy as to whether people with intermediate deficiency of AAT, specifically the Pi MZ phenotype, have an increased risk of developing clinically important chronic obstructive pulmonary diseases. The question has been approached by two general types of studies.

In the first type of study Pi phenotypes were obtained in a series of patients with chronic obstructive pulmonary disease and in a series of normal controls. The frequency of the Pi MZ or partial deficiency phenotype was compared in the two groups. In several studies the frequency of partial deficiency was significantly increased in the COPD group. In one study 18% of COPD patients had partial deficiency whereas 5% of the control group showed intermediate levels of AAT. In another study 4.9% of the COPD patients had a Pi MZ phenotype whereas 1.9% of the control group had that type. These series are to be contrasted with a number of others in which the frequency of Pi MZ was not significantly different in COPD and control groups (8).

In the other type of study a series of persons with MZ Pi types were studied for the presence of lung changes. In several of these studies abnormalities of expiratory flow rate, lung elastic recoil, and xenon ventilation scans were found but in most of those patients with abnormalities in these tests no clinical emphysema was present (9). Although the results are presently inconclusive they suggest that persons with Pi MZ may have a slightly increased risk of developing emphysema but that risk is nowhere near the 70–80% risk of persons with severe deficiency.

Liver disease

Severe deficiency of AAT was discovered in some children with neonatal hepatitis or cirrhosis independent of the earlier association between severe deficiency and emphysema (10). In the presence or absence of clinical liver disease the hepatocytes in patients with either one or two Z alleles for AAT show PAS positive globules which on electron microscopy can be located within the rough and the smooth endoplasmic reticulum. Fluorisceinated antiserum specific for AAT shows that these globules are antigenically identical to AAT. This accumulation is more dramatic in patients with Pi ZZ but even in those patients not all cells are involved.

Recent reports present information on the natural history of liver disease in patients with severe deficiency of AAT. In Sweden an antibody test was used to quantitate AAT in 200,000 newborns (11). The 190 infants with less than 40% of the standard quantity of serum AAT were Pi typed. 120 had PiZ and 48 had Pi SZ. These infants were then studied prospectively for evidence of liver disease at 3 and 6 months by clinical examination and by measurements of bilirubin, alkaline phosphatase, SGPT and glutamyl transpeptidase. Seven percent of the Pi ZZ infants had clinical and laboratory evidence of obstructive jaundice with hepatosplenomegaly at the first examination at about 3 months of age. Three percent had some clinical jaundice and another 6% had variable symptoms that caused liver disease to be suspected in the first half year of life but complete testing had not been done. About half the remaining Pi Z children had chemical abnormalities indicating damage to the hepatocytes or bile ducts or both. At 6 months of age all these children were healthy and showed at the most only mild signs of liver disease. The design of the ascertainment procedure was such that probably all of the Pi Z newborns were detected. The study also detected 48 newborns who had Pi SZ. This sample probably represents only a fraction of the Pi SZ offspring in the newborn population because several of the Pi SZ newborns were expected to have an AAT serum level greater than the cut-off used for the study. In the 48 infants who were studied none had liver disease and abnormalities of the biochemical indices were rare. In other series infants with Pi SZ and neonatal hepatitis have been identified. Nevertheless, this important study has developed and will continue to produce important prospective information on the risk of liver disease in childhood in patients with Pi ZZ and other forms of severe deficiency of AAT.

When the association of childhood cirrhosis and severe deficiency of AAT was first identified these patients were thought to have a uniformly gloomy prognosis. However, a recent series of 18 patients present a somewhat more optimistic view (12).

In this series 14 patients presented with neonatal hepatitis and an additional four presented with hepatosplenomegaly without jaundice. In those patients in whom liver tissue had been obtained at the time of hepatitis a giant cell hepatitis histologic picture was identified. Among the 18 patients, four had died of liver failure by the ages of 5–12 years. On the other hand, four were well at greater than 13 years and showed no clinical or chemical indications of liver disease. The early course in these patients gave little indication of which patients would do well and which would do poorly. The only indication was that cirrhosis without a previous history of jaundice might be a bad prognostic sign.

A summary of idiopathic neonatal hepatitis cases suggests that severe deficiency of AAT may account for 25%. In adults with severe deficiency of AAT liver disease also occurs with a frequency greater than expected from population frequencies. In one series of 13 autopsy cases 5 patients had cirrhosis and 3 fibrosis of the liver. An additional unexpected finding, and one that has been confirmed in other series, was the observation that three of these eight patients with liver disease also had a hepatoma. Siblings who both had Pi ZZ, neonatal hepatitis, and childhood emphysema have been reported. In a recently reported series of 469 patients with hepatobiliary disease, 410 of whom were over 20 years old, only 5(1%) had Pi ZZ and all 5 had had neonatal liver disease (13). Partial deficiency of AAT was more common in the control group than in the liver disease patients. It was concluded that severe deficiency of AAT was an important possibility only in liver disease patients who are children, who had neonatal hepatitis, or in whom no other etiology is apparent.

Chromosomal abnormalities

Since more than 20 different alleles at the AAT locus have been identified a very large number of different Pi types or combinations of these alleles is possible and many of them have been detected. Reports continue to appear of the association of increased frequencies of specific Pi types or of heterozygote Pi types with various clinical conditions.

In one series of patients who showed chromosomal mosaicism for sex chromosome abnormalities there was an increased frequency of several different kinds of heterozygote Pi types. In another series of patients with trisomy 21 and Down syndrome an increased frequency of heterozygote types was also identified. The significance of these observations remains to be established.

Respiratory distress syndrome

In infants with the respiratory distress syndrome serum levels of AAT undergo a transient decrease. The patients who succumbed to the respiratory distress had the lowest AAT levels and those who recovered generally elevated their AATs to normal neonatal levels within the first day or two of life.

Studies of lung in this condition show that AAT is deposited in the pulmonary alveolar membrane. The decrease in AAT is not specific for that protein and several other proteins undergo a transient depression as well. The Pi type in patients with the respiratory distress syndrome is M indicating that the transient depression in serum AAT levels is not due to the same genetic defect that produces stable deficiency in the Pi SZ and ZZ cases.

Summary

Much remains to be learned about the pathogenesis of the diseases caused by AAT deficiency. When the specific proteases are found whose uninhibited activity results in emphysema, synthetic inhibitors can be sought as possible replacement therapy for patients lacking the natural molecule. The identification of risk factors, in addition to smoking, that act synergistically with AAT deficiency might permit environmental manipulations aimed at reducing the likelihood or severity of emphysema.

Neonatal hepatitis due to AAT deficiency seems to occur more frequently in the siblings of patients who also have hepatitis due to severe deficiency. This familial clustering suggests the hepatitis promoting action of a second genetic factor in addition to AAT deficiency. Understanding of this factor may be helpful in reducing the risk of liver disease in patients with low amounts of AAT.

Finally, the discovery of AAT deficiency in a few patients with emphysema has stimulated the study of the rôle of proteolysis in chronic obstructive pulmonary disease, and may lead to a better understanding of disease pathogenesis in the vast majority of emphysema patients who do not have AAT deficiency.

References

1. Eriksson, S.: Pulmonary Emphysema and Alpha-1-Antitrypsin Deficiency, Acta Med Scand 175:197, 1964.
2. Fagerhol, M. K. and Laurell, C. B.: The Pi System—Inherited Variants of Serum Alpha-1-Antitrypsin. In *Progress in Medical Genetics*. Edited by A. G. Steinberg and A. G. Bearn. Grune & Stratton, New York 1970, vol. 7, p. 96.
3. Yoshida, A., Lieberman, J., Gaidulis, L., and Ewing, C.: Molecular Abnormality of Human Alpha$_1$-Antitrypsin Variant (Pi-ZZ) Associated with Plasma Activity Deficiency, Proc Nat Acad Sci USA 73:1324, 1976.
4. Owen, M. C. and Carrell, R. W.: Alpha-1-Antitrypsin: Molecular Abnormality of S. Variant, Br Med J 1:130, 1976.
5. Galdston, M., Janoff, A., and Davis, A. L.: Familial Variation of Leukocyte Lysosomal Protease and Serum Alpha-1-Antitrypsin as Determinants in Chronic Obstructive Pulmonary Disease, Am Rev Resp Dis 107:718, 1973.
6. Kueppers, F. and Bearn, A. G.: A Possible Approach to the Association of Hereditary Alpha-1-Antitrypsin Deficiency and Pulmonary Emphysema, Proc Soc Exp Biol Med 121:1207, 1966.
7. Kueppers, F. and Black, L. F.: Alpha-1-Antitrypsin and Its Deficiency, Am Rev Resp Dis 110:176, 1974.
8. Cox, D. W., Hoeppner, V. H., and Levison, H.: Protease Inhibitors in Patients with Chronic Obstructive Pulmonary Disease: the Alpha$_1$-Antitrypsin Heterozygote Controversy, Am Rev Resp Dis 113:601, 1976.

9. Hall, W. J., Hyde, R. W., Schwartz, R. H., Mudholkar, G. S., Webb, D. R., Chaubey, Y. P., and Townes, P. L.: Pulmonary Abnormalities in Intermediate Alpha-1-Antitrypsin Deficiency, J Clin Invest 58:1069, 1976.
10. Sharp, H. L., Bridges, R. A., Krivit, W., and Freier, E. F.: Cirrhosis Associated with Alpha-1-Antitrypsin Deficiency: A Previously Unrecognized Inherited Disorder, J Lab Clin Med 73:934, 1969.
11. Sveger, T.: Liver Disease in Alpha-1-Antitrypsin Deficiency Detected by Screening of 200,000 Infants, N Engl J Med 294:1316, 1976.
12. Moroz, S. P., Cutz, E., Cox, D. W., and Sass-Kortsak, A.: Liver Disease Associated with Alpha$_1$-Antitrypsin Deficiency in Childhood, J Pediatr 88:19, 1976.
13. Fisher, R. L., Taylor, L., and Sherlock, S.: Alpha-1-Antitrypsin Deficiency in Liver Disease: The Extent of the Problem, Gastroenterology 71:646, 1976.

The Mount Sinai Journal of Medicine
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Increase of the Alpha$_1$-Antitrypsin in Lung Cancers

GIUSEPPI DADDI

Serum level determination of ATT for some years has been widespread practice as a result of the finding that in certain cases of emphysema, above all in primary emphysema, there is a deficiency of this enzyme. Consequently, attention has been given almost exclusively to detection of such ATT deficiency. Recently we have tried to discover the behavior of this substance in lung cancer, a disease not rarely accompanying pulmonary emphysema. We employed radial immunodiffusion according to the method of G. Mancini, which allows a sufficiently rapid and accurate quantitative determination of ATT. One-hundred cases of lung cancer of differing histotype and degree of growth have thus far been observed. The patients were both male and female.

The results obtained have been unanimous in demonstrating a distinct increase of ATT as compared with normal average values of approximately 220 mg per 100 ml. In all the cases studied, the enzyme proved to be present in considerably higher quantities, up to more than 820 mg per 100 ml, with an average of 625 mg % ml in men and 608 mg % ml in women.

Patients in the control group suffering from lung disorders, other than neoplasms, gave normal values.

A careful study of our patients has shown that none of them evidenced conditions that could cause an increase of ATT. The increase of ATT would seem to be attributable exclusively to the presence of lung cancer.

During our study, we learned of the work of Harris et al (1974) who in a large study reported findings similar to our own. Other authors have incidentally observed the same phenomenon in a small number of cases (e.g., Hass and coworkers, 8 cases). This concordance of results confirms that in lung cancer there is in effect a marked increase of ATT.

Our investigations are continuing in order more precisely to define the characteristics and significance of the phenomenon. We are investigating the effects on ATT levels of various forms of therapy and, above all, the differential diagnostic importance of ATT determinations, particularly since, as already stated, a certain number of lung cancers develop in patients suffering from emphysema.

The Mount Sinai Journal of Medicine
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Traitement de la Tuberculose

JACQUES CHRETIEN

Base du Traitement Antituberculeux

Quelles que soient la topographie, l'étendue, l'étape évolutive des lésions, toute tuberculose requiert un traitement anti-infectieux spécifique visant à stériliser l'organisme de bacilles qui s'y développent. Ce traitement spécifique est capable d'assurer cette stérilisation dans la totalité des cas (1).

La statégie thérapeutique est fondée sur la connaissance des particularités biologiques des bacilles et du mode d'action des drogues antibacillaires.

Le bacille de Koch (BK), mycobactérie tuberculeuse, est un aérobie strict (d'où son faible développement dans les lésions solides et sa pullulation dans les cavités aérées du poumon).

La multiplication est lente—toutes les 20 heures environ, ce qui l'oppose aux germes dits banaux de multiplication rapide et donc beaucoup plus accessibles à une thérapeutique basée sur une entrave à cette multiplication. Le taux de mutation est élevé: dans une souche de BK sauvages (= non traités) toute la population bacillaire est sensible à tous les antituberculeux (90% des cas), mais il existe au moins 1 bacille sur 100 000 qui diffère du reste de la souche et qui est génétiquement résistant à l'Isoniazide. C'est un bacille "variant"; aussi appelé "mutant-résistant" (2). Les mutants-R peuvent aussi naître, de temps en temps, de la multiplication des bacilles sensibles.

Le nombre de mutants-résistants d'emblée existant initialement dans la souche sauvage est différent selon les drogues (Tableau I).

La mutation-sélection survient si la souche est soumise à une monothérapie qui empêche la reproduction des bacilles sensibles mais laisse survivre et se multiplier les variants.

La richesse de la population bacillaire dans les lésions est donc une notion essentielle à connaître pour évaluer le risque d'apparition d'une résistance et pour orienter la thérapeutique (Tableau II).

Dans une lésion cavitaire qui contient 10^8 bacilles sensibles à l'INH et qui est traitée par INH seul, il restera 10^3 bacilles résistants, qui continueront à se multiplier et remplaceront peu à peu la population bacillaire initialement sensible par une population totalement résistante.

Or, il n'y a qu'une solution pour détruire les mutants-résistants qui se trouvent dans toute souche sensible à une drogue, c'est d'utiliser une drogue anti-bacillaire différente, capable de les détruire.

En effet, s'il y a dans un million de bacilles 1 mutant-résistant à chacun des 2 antibacillaires associés, la probabilité que ce mutant soit résistant à chacun des deux n'est que de: $10^{-6} \times 10^{-6} = 10^{-12}$.

Cette prévision théorique de l'efficacité d'une association médicamenteuse dans la prévention de la résistance a été largement confirmée par l'expérimentation et la clinique; c'est la base de la chimiothérapie associée (Tableau III).

TABLEAU I

Nombre de Mutants-résistants selon les Drogues Antibacillaires

Ethambutol	Ethionamide	Streptomycine	Isoniazide	Rifampicine
1 pour 1,000 mutants-résistants (10^3)	1 pour 1,000 (10^3)	1 pour 100,000 (10^5)	1 pour 100,000 (10^5)	1 pour 100 millions (10^8)

TABLEAU II

Nombre de Bacilles selon la Nature Histo-pathologique des Lésions Tuberculeuses

Foyer caséeux fermé	Foyer caséeux ouvert	Caverne
	(caséum ramolli)	
10 à 10^3 bacilles	10^4 à 10^6 bacilles	10^7 à 10^9 bacilles

TABLEAU III

Nombre comparé de Mutants-Résistants prévisibles en Monothérapie et en Bithérapie d'une Lésion cavitaire (10^8 Bacilles)

Traitement par:	Taux de mutation	Nombre de mutants-résistants
I.N.H. seul	1 p. 10^5	10^3
S.M.Y. seule	1 p. 10^5	10^3
I.N.H. + S.M.Y.	$1/10^5 \cdot 1/10^5 = 1/10^{10}$	0

La probabilité de voir apparaître des bacilles résistants est donc *fonction de la richesse de la population bacillaire, du taux initial de mutants-résistants, du choix thérapeutique.*

Les antibiotiques (ATB) peuvent être classés selon leur mode d'action en 3 groupes:

1) *Les drogues ayant une activité bactéricide et agissant sur les BK intracellulaires à la même concentration que sur les BK extracellulaires.* Cette deuxième caractéristique est fondamentale en raison du fait qu'une proportion importante de bacilles est intra-cellulaire, au sein des macrophages. Ce groupe comporte:isoniazide (INH), rifampicine (AMP), ethionamide (ETA), ethambutol (EMB), pyrazinamide (PZA), cycloserine (CS).

2) *Les antibiotiques bactéricides exigeant une concentration environ 10 fois plus forte pour agir sur les BK intra-cellulaires*, ce sont : streptomycine (SMY), kanamycine (Kana), viomycine (Vio), capreomycine.

3) *Les antibiotiques seulement bactériostatiques*, situés à bas niveau dans l'échelle d'efficacité. Ce sont: para-amino-salicylate de sodium (PAS), thiacetazone (TB), tetracycline.

Ensuite intervient un classement selon le "coefficient de dépassement": in vitro, une certaine quantité d'ATB est nécessaire pour inhiber la croissance des bacilles, c'est la concentration minimale inhibitrice = CMI. Elle est variable selon les drogues antibacillaires. Dans l'organisme, il faut aussi un certain niveau d'ATB dans le sérum pour obtenir l'inhibition: c'est le taux sérique efficace, qu'on peut aussi exprimer d'une autre façon par le dilution inhibitrice minimale: DIM. Le taux sérique de la drogue antibacillaire est d'autant plus efficace qu'il est supérieur à la CMI; en effet, la CMI, mesurée, in vitro, ne tient pas compte des variations individuelles de virulence de la souche infectante, ni des variations individuelles du taux sérique pour une même dose administrée. Cette marge de fluctuations complexes est couverte seulement par les ATB dont le taux sérique est très supérieur à la CMI.

Le rapport entre les deux concentrations est appelé le coefficient de dépassement moyen:

$$\frac{\text{Taux sérique moyen}}{\text{CMI}} = \text{C D m}$$

Le C D m indique donc combien de fois le taux sanguin obtenu chez l'homme avec les doses thérapeutiques habituelles dépasse les concentrations nécessaires pour inhiber le BK in vitro. Ce coefficient est de: 74 pour la rifampicine, 27 pour l'Isoniazide (INH), 6,1 pour l'ethionamide, 4,7 pour l'ethambutol, 3 pour la cycloserine. La première place dans la hiérarchie des drogues antituberculeuses revient donc, de loin, à la rifampicine (3).

Intervient également la pénétration des ATB dans les foyers tuberculeux. Ce n'est pas dans le sang mais dans les foyers tuberculeux que se trouvent les bacilles (Tableau IV). Les taux sanguins ne sont donc pas un reflet tout à fait fidèle des taux existant dans les lésions, mais, compte-tenu du coefficient de dépassement, la Rifampicine garde bien la lère place et l'INH la seconde.

Enfin, l'obtention d'un "pic sérique" élevé est nécessaire et il est à présent démontré que c'est ce "pic élevé" de concentration sérique et non la durée totale de la présence de concentrations inhibitrices dans le sérum qui donne au médicament son meilleur rendement. Pour obtenir ce pic élevé, il ne faut donc pas répartir les doses en plusieurs prises dans la journée mais les donner en une seule prise qui assure le pic de beaucoup le plus élevé(4).

En corollaire: le fait d'associer plusieurs antibacillaires ne permet pas de diminuer à volonté la dose de chacun d'eux.

On risquerait fort de ne pas atteindre le pic de concentration nécessaire à un effet optimum, voire même d'être en dessous de la concentration sérique efficace.

En résumé, l'Antibacillaire, pour agir efficacement doit donc:

– être bactéricide

– l'être à la même concentration pour les BK intra-cellulaires que pour les BK extra-cellulaires.

– avoir un coefficient de dépassement élevé

– pénétrer dans les lésions à une concentration efficace

– être administré de façon à produire un pic de concentration élevé.

Modalités pratiques: Des règles impérieuses découlent, dans la pratique,

TABLEAU IV

Rapport entre les Taux d'ATB dans les Lésions et les Taux Sanguins étudiés pour 3 ATB

	$\frac{\text{Taux Poumon}}{\text{Taux sérique}}$	$\frac{\text{Taux caséum}}{\text{Taux sérique}}$	$\frac{\text{Taux intra-cavitaire}}{\text{Taux sérique}}$
Rifampicine	1,6	0,35	1,3
Isoniazide	0,6 à 0,8	0,28	0,5
Ethionamide	0,9	0,69	0,77

de la connaissance de la multiplication bacillaire et des conditions d'action des drogues antibacillaires. Ces règles fondamentales, au nombre de sept sont schématisées dans le Tableau V. Les contre-indications des antituberculeux les plus souvent employés sont résumées dans le Tableau VI.

1. *Posologie et mode d'administration.*

Les posologies quotidiennes sont les suivantes:

a. Rifampicine: Prise per os, la dose est de 10 mg/kg de poids corporel (en pratique 600 mg pour des adultes de 50 à 80 kg), soit 2 gélules de 300 mg de Rifadine* ou de Rimactan*. Chez l'enfant avant 10 ans, la dose est de 12 à 15 mg/kg (4, 5, 15).

b. Isoniazide: Les doses sont à établir d'après la concentration sérique obtenue 3 heures après la prise isolée de 300 mg du médicament; cette concentration est fonction de l'acétylation hépatique des patients.

Une concentration sérique comprise entre 1 et 2 micro-grammes par mililitre est nécessaire et suffisante (6, 7).

En l'absence de possibilité de dosage sérique et en cas d'association avec la Rifampicine, la posologie ne doit pas dépasser 7, 5 mg/kg pour éviter tout accident hépatique (8, 9, 10). La prescription parallèle de vitamine B6 est nécessaire chez les alcooliques, les patients dénutris et les diabétiques.

c. Ethambutol: La dose est de 25 mg/kg pendant toute la durée du traitement (11, 4).

d. *Streptomycine*: Chez l'adulte, la posologie quotidienne est de 1 g/jour, chez l'enfant ainsi que chez les adultes de faible poids corporel (cachexisme) elle est de 30 à 50 mg/kg. L'administration est effectuée par voie intramusculaire.

e. Ethionamide: Administré généralement par voie orale, rarement en intra-veineuse (perfusion possible dans du sérum bicarbonaté isotonique), la voie rectale est à proscrire, la posologie est de 15 mg/kg (750 mg à l g par jour).

f. Pyrazinamide (Piraldine*): Employé en priorité en cas de résistance des bacilles aux antibiotiques majeurs (l'altération des fonctions hépatiques étant une contre-indication) elle est prescrite à la dose de 50 mg/jour. Le produit commercialisé en France sous le nom de Piazoline* comporte le dérivé morphazinamide moins actif et plus toxique et doit être évité. (12, 13).

2. *Schémas thérapeutiques.*

Plusieurs schémas thérapeutiques sont possibles suivant le degré d'activité des antibiotiques, leurs contre-indications éventuelles liées au terrain, l'existence de résistance ou d'intolérance.

Tous doivent comporter une triple association jusqu'au résultat de l'antibiogramme ou en son absence durant les 3 premiers mois de traitement.

3. *Primo-traitement (Tableau VII).*

Deux éventualités sont à envisager:

a. *Bacilles supposés sensibles* (il n'y a pas de tuberculose traitée dans l'environnement immédiat du patient et pas de contamination connue à bacilles résistants).

Dans ce cas, une association de trois antituberculeux est justifiée, et la meilleure est *Rifampicine, Rimifon et Ethambutol.* Dans la deuxième phase du traitement, il faut préférer le binôme Rifampycine-Rimifon.

TABLEAU V

Regles Pratiques du Traitement de la Tuberculose

Les bacilles peuvent être résistants
– d'emblée (résist. primaire)
– après traitem. antérieur (résist. secondaire)

d'où **1ère règle** → Antibiogramme

Une défaillance organique peut contre-indiquer le traitement

d'où **2ème règle** → Bilan pré-thérapeutique bio-clinique systématique

Foie:	B.S.P. transaminases (SGPT), bilirubine totale
Rein:	Urée sanguine, créatininémie
Oeil:	Vision des couleurs, champ visuel, recherche de névrite optique rétro-bulbaire pré-existante, ou autre contre-indication.
Oreille:	Audiogramme (en cas d'emploi de la Streptomycine).

Emergence de bacilles mutants-résistants.

d'où **3ème règle** → Association indispensable

de *trois* ATB *majeurs* en phase initiale *puis deux*, après titrage (ou après 3 mois)

Nécessité de concentration plasmatique efficace et d'un pic sérique élevé.

d'où **4ème règle** → Doses adéquates — dosage INH sérique
→ En prise unique

Permanence indispensable de concentration efficace.

d'où **5ème règle** → Temps de traitement suffisant
→ Continuité absolue

Des règles 3, 4 et 5, découle

6ème règle → Conditionner le malade à la prise unique matinale de la dose totale

Les ATB peuvent donner des accidents toxiques

d'où **7ème règle** → Surveillance bio-clinique régulière

L'association de Rifampicine, Isoniazid, Streptomycine est à *proscrire* car 2, 5% des souches sont résistantes à la fois au Rimifon et à la Streptomycine avec *le risque dans 2, 5% des cas de perdre l'activité de la Rifampicine.*

Il faut noter en outre le risque de résistance à l'INH seul de 5% et à la Streptomycine seule de 7, 6%.

b. *Bacilles suspects de résistance primaire* (contact avec un tuberculeux traité, contamination hospitalière . . .)

– La première précaution avant le choix du traitement est de répéter les recherches de bacilles (mise en route de 6 cultures au minimum).

– La meilleure association, qui comporte le moins de risque de résistance primaire est Rifampicine + Ethambutol (taux connu = 0) à laquelle on adjoindra INH + Streptomycine pour augmenter les chances d'avoir 3 antibiotiques actifs. Sur la vue de l'antibiogramme, les modalités du traitement seront modifiées. Seront éventuellement stoppés Rimifon et/ou Streptomycine.

4. *Traitement de rechute (retraitement).*

Le choix des antibiotiques en attendant le résultat de l'antibiogramme est

TABLEAU VI

Contre-Indications des Antibacillaires

AMP + INH, EMB
Absolue: – Atteinte de la cellule hépatique, prouvée par bilan pré-thérapeutique
– Cirrhose confirmée, décompensée. Ictère par rétention
Relative: – Insuffisance rénale
– Denutris graves et malades ≥80 ans (commencer par doses réduites)
INH
Absolue: – Maladie mentale avec antécédents de crise maniaco-dépressive
Relative: – Antécédents d'affections mentales mineures et de convulsions
Rifadine
Relative: – Grossesse au début (3 premiers mois)
Ethambutol
Absolue: – Névrite optique
– Insuffisance rénale
– Perte préalable d'un des deux yeux
Relative: – Insuffisance rénale modérée: urée sanguine jusqu'à 1 g (dose réduite et surveillance accrue)
Streptomycine
Absolue: – Atteinte auditive pré-existante
– Insuffisance rénale: urée sanguine ≥0,60 g/l
– Allergie à la Streptomycine.

Toutes les contre-indications relatives sont à discuter en fonction de chaque cas, et en fonction de la gravité de l'atteinte tuberculeuse.

Chaque fois qu'une contre-indication est discutée pour une drogue donnée, le choix du traitement relève du milieu spécialisé.

TABLEAU VII

Associations possibles des Anti-Tuberculeux (Primo-Traitement)

Bacilles Supposés Sensibles
Ordre Préférentiel

AMP: Rifampicine
INH: Isoniazide
EMB: Ethambutol
SMY: Streptomycine
ETA: Ethionamide

1° phase	AMP INH EMB		INH EMB SMY	AMP INH ETA		INH SMY ETA
2° phase	AMP INH	INH EMB	INH EMB	AMP INH	INH ETA	ETA INH

dicté par les médicaments antérieurement reçus. Il faut prescrire 3 et si possible 4 antibiotiques jamais prescrits auparavant.

L'existence ou la suspicion de résistance exige un recours spécialisé pour éviter toute erreur irréparable dans l'orientation thérapeutique.

5. *Règles d'exécution du traitement.*

Elles sont à respecter strictement et découlent des données précédemment énoncées. Elles comportent:

—*un bilan pré-thérapeutique*, en particulier hépatique, rénal et ophtalmologique, éventuellement auditif, pour rechercher d'éventuelles contre-indications de principe à tel ou tel antibiotique (14, 9).

—*la prise unique matinale* (à jeun, 40 minutes avant le premier repas) de la totalité de la posologie quotidienne des médicaments.

—la prise quotidienne régulière sans aucun manque.

—la poursuite du traitement, actuellement sur une durée minimum de 12 mois, prolongée au besoin en fonction de la gravité de l'affection.

—la surveillance de l'efficacité du traitement sur des *critères bactériologiques* (répétition des examens directs et des cultures à intervalles réguliers).

—le dépistage précoce enfin, d'éventuelles complications iatrogènes propres à chacun des antibiotiques.

6. *Cas particuliers.*

a. La corticothérapie associée au traitement antituberculeux ne sera jamais systématique même en cas d'épanchement pleural.

b. Un traitement local est parfois utile (localisations ganglionnaires externes). Est utilisée en cas de nécessité, l'instillation locale d'Isoniazide, de Streptomycine et d'une Rifampicine (Rifocine*).

c. L'association Rifampicine-contraceptifs oraux par suite d'inductions enzymatiques hépatiques peut avoir un effet contrariant sur ces derniers avec possibilité de grossesse. Les patientes doivent en être informées avec une adaptation de la contraception (18, 19, 20).

La Rifampicine par principe n'est pas prescrite lors des 3 premiers mois de la grossesse sauf nécessité absolue; par la suite, la surveillance des fonctions hépatiques doit être très stricte.

Conclusion

Rigueur dans le choix des antituberculeux, qui repose sur des données bactériologiques et pharmacologiques, respect strict des règles d'exécution et de surveillance du traitement, trop souvent négligés, sont indispensables pour éviter la survenue d'accidents iatrogènes, parfois graves, prévenir la multiplication de mutants-résitants et obtenir la guérison de la tuberculose. Toute erreur est en effet généralement irréparable dans la mise en route d'un premier traitement.

References

1. Rouillon A., Perdrizet S., Parrot R.: La transmission du bacille tuberculeux. L'effet des antibiotiques. Rev Fr Mal Resp 4:241, 1976.
2. Canetti G., Le Lirzin M., Gay Ph., Thibier R. et coll.: La résistance primaire dans la tuberculose pulmonaire de l'adulte en France. Rev Tuberc Pneumol 36:337, 1972.
3. Canetti G., Kaczmierzak A., Le Lirzin M.: Un classement des drogues antituberculeuses selon les taux sanguins chez l'homme. Rev Tuberc Pneumol 35:5, 1971.
4. Papillon F.: Conditions d'emplois et résultats du traitement par la Rifampicine et l'Ethambutol. Vie Med 21:2635, 1973.
5. Porven G., Canetti G.: Le taux de Rifampicine dans le sérum de l'homme. Rev Tuberc Pneumol 32:707, 1968.
6. Thenault D., Saltiel J. C., Houin G., Vivien J. N., Tillement J. P., Chretien J.: Comparaison des deux méthodes de dosage de l'INH sérique. (étude chez 50 patients) 1976, à paraître.
7. Vivien J. N., Thibier R., Lepeuple A.: Pharmacocinétique de l'INH dans la race blanche. Rev Fr Mal Resp 1:753, 1973.
8. Isoniazid liver injury: clinical spectrum, pathology and probable pathogenesis. NIH Conference. Ann Intern Med 84:181, 1976.
9. Morere P., Stain J. P., Bourreille J., Nouvet T. G.: Ictère et cytolyse chez les malades recevant à la fois Rifampicine et Isoniazide. Rev Tuberc Pneumol 34:1110, 1970.
10. Smith J., Tyrell W. F., Gowa A., Allan G. W., Lees A. W.: Hepatotoxicity in Rifampicin Isoniazid treated patients related to their rate of Isoniazid inactivation. Chest Dis 61:587, 1972.
11. Acquisitions récentes dans le traitement de la tuberculose. G M de France 1972, 79.
12. Fouquet J., Teyssier L. A.: Le pyrazinamide et la morphazinamide dans le traitement des tuberculoses à bacilles résistants aux antibiotiques majeurs. Rev Tuberc 28:846, 1964.
13. Rist N.: Le pyrazinamide. Rev Tuberc 26:752, 1962.
14. Leibold J. E. The ocular toxicity of Ethambutol. Ann N Y Acad Sci 135:904, 1966.
15. Chretien J., Pariente R.: Le traitement des pleurésies par l'hormonothérapie hypophysaire surrénalienne. Critique de son emploi systématique. Discussion de ses indications. In *Entretiens de Bichat*, Vol 1 et in la Semaine Thérapeutique 1962, 6:529.
16. Chretien J., Hirsch A., Papiernik M., Saint Paul M., Bonnaud G.: Note préliminaire concernant l'exploration systématique de certaines réactions immunitaires loco-régionales au cours des épanchements pleuraux. Ann Med Interne 121:635, 1970.
17. Chretien J.: Emploi de l'A.C.T.H. dans les pleurésies. In *Colloque thérapeutique* CIBA. Paris Mars 1970, 105–109.
18. Boltt H. M., Kappus H., Bolt M.: Rifampicin and oral contraception. Lancet 2:232, 1974.
19. Hirsch A., Tillement J. P., Chretien J.: Effets contrariants de la Rifampicine sur les contraceptifs oraux: A propos de trois grossesses non désirées observées chez deux malades. Rev Fr Mal Resp 3:174, 1975.
20. Skolnick J. L., Stoler B. S., Katz D. B., Anderson W. H.: Rifampicin oral contraceptive and pregnancy. JAMA 236:1382, 1976.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Kartagener's Syndrome – A Ciliary Immotility Syndrome

BJÖRN MOSSBERG AND ÅKE HANNGREN

Introduction

Among the congenital syndromes met within the field of pulmonary medicine, Kartagener's syndrome is without doubt one of the most spectacular, with its curious association of situs inversus, chronic sinusitis, and bronchiectasis. Originally described in 1933 by Kartagener of Switzerland (1), several hundred cases have since been reported in the literature and many theories of its pathogenesis have been proposed. Recent data sheds new light to help solve the mystery of Kartagener's syndrome.

Historical Background

The first description of a case of bronchiectasis in a patient with situs inversus appeared in a paper by Siewert in 1903 (2). A few scattered case reports followed but Kartagener's paper published in 1933 was the first to receive widespread attention. He described four patients with a history of productive cough since early childhood, chronic sinusitis, nasal polyposis, and complete situs inversus; bronchiectasis was demonstrated in all four patients by means of bronchography. He also presented evidence on the frequency of situs inversus associated with bronchiectasis in support of his opinion that the combination was not merely coincidental. Kartagener later described several more instances of the syndrome and has repeatedly reviewed the literature and discussed its etiology (3). He suggested that the bronchiectasis was congenital, an opinion shared by the famous German surgeon, Sauerbruch.

The combination of situs inversus, chronic sinusitis and bronchiectasis led to the name "Kartagener's triad," but since it is also characterized by rhinitis, nasal polyps, chronic or recurrent otitis media, and absent or underdeveloped frontal sinuses, the term 'syndrome' seems more appropriate. Bronchiectasis is not always present; indeed, chronic bronchitis is a more constant feature.

Frequency

In the first paper in the English language, Adams & Churchill (4), pointed out that the prevalence of bronchiectasis among patients admitted to the Massachusetts General Hospital since 1886 was 0.306 per cent. Among the 23 cases of situs inversus recorded in the hospital during the same period the figure for bronchiectasis was 21.7 percent. Thus, about one fifth of the cases with situs inversus had Kartagener's syndrome. The figures bolstered the view that the association of situs inversus and bronchiectasis is not coincidental. The authors also pointed out that most patients with bronchiectasis also had signs of infection of the paranasal sinuses and that little importance could be assigned to the concurrence of these two components in Kartagener's syndrome (4). In 1943 Olsen analysed 85 cases with dextrocardia encountered at the Mayo Clinic and noted among them a frequency of bronchiectasis of 16.5 percent (5). Although the association with bronchiectasis is high in situs inversus, the contribution of these patients to the overall pool of bronchiectatic patients is small. Lindskog & Hubbel in an analysis of 215 cases of bronchiectasis found only three patients with Kartagener's syndrome (6).

Genetic Pattern

In 1938, Cockayne (7) reviewed the literature on situs inversus and estimated the prevalence of transposition of the viscera to lie between 1:9000 and 1:24000. He presented convincing evidence that complete transposition is inherited as an autosomal recessive gene. Situs inversus has been recorded in most parts of the world. It is reported to be twice as common in Japan as elsewhere. Katsuhara et al reported the prevalence of situs inversus in a Japanese population to be 1:4100, and this abnormality was associated with bronchiectasis in 25 percent of the patients. The high frequency of situs inversus is possibly a result of the high rate of consanguineous marriages in Japan (18). Torgersen calculated transposition of the viscera to be approximately 1:8000 in a continuous series of more than 300,000 individuals examined by mass chest x-ray in Norway (8). He collected a total of 129 individuals with situs inversus, most of whom had complete transposition. One hundred and twenty-three of the individuals had 573 brothers and sisters and among these situs inversus was found in only six – very far from the ratio of 1:3 expected, if the condition was due to a recessive gene. This author found a higher than normal frequency of consanguinity in parents, and this would fit with the concept of a recessive gene. Approximately 10 percent of his 129 situs inversus patients had respiratory tract symptoms as did 25 percent of their siblings, a finding that fits well with a recessive mode of inheritance of a constitution with a vulnerability to infections of the nose and bronchi. Torgersen also found a higher than expected rate of respiratory tract disease in the parents of these subjects, indicating a dominant mode of inheritance, so he was unable to supply a simple genetic explanation. He concluded that inheritance was probably dominant but in a complex way; the gene or genes causing bronchiectasis and nasal polyps could sometimes cause transposition of the viscera.

Torgersen's study showed that siblings of subjects with Kartagener's syndrome often have disease of the nose and bronchi with or without situs inversus. Bergstrom et al (9) described a family with six siblings; two had Kartagener's syndrome and two had only bronchiectasis and chronic sinusitis. Similar families with different combinations of the syndrome are commonly reported (10–18). Holmes et al (16), have neatly summarized the available information on genetics of Kartagener's syndrome. In describing 13 subjects with Kartagener's syndrome from eight different families they also found in the siblings a prevalence of situs inversus or sinopulmonary disease which fitted well with the concept of recessive autosomal inheritance of a gene causing sinopulmonary disease, sometimes causing situs inversus. As further support for the theory of an autosomal recessive gene they described its occurrence in only one generation and in monozygotic twins, the absence of any sexual predisposition and the high frequency of consanguinity among the parents. The main contradiction to this concept seemed to be Torgersen's observation of a high incidence of respiratory tract infection among the parents.

Congenital Associations

Situs inversus is often associated with various other congenital malformations (7, 19), but this is not as evident with Kartagener's syndrome (5, 20). There are, however, a number of scattered reports on congenital malformations observed in subjects with Kartagener's syndrome including heart disease (9, 16, 21), abnormalities of the genitourinary tract (16, 22), anomalous bronchial division (13, 17), dislocated hip (18), the Paterson-Brown-Kelly syndrome (23). It is possible that some of these malformations are rare expressions of the gene or genes causing Kartagener's syndrome but coincidence is also likely in the offspring of consanguinous marriage. Kartagener's syndrome has occasionally been recorded with cystic fibrosis (24), a maximum of bad luck, but there is little difficulty in distinguishing them for they have different clinical patterns and bronchial histology (16). Subjects with Kartagener's syndrome usually live a relatively normal life and the syndrome is also compatible with a normal life span. The oldest subject recorded was 88 years old (25).

Pathogenesis and Etiology

This has mainly concerned the origin of situs inversus and of bronchiectasis separately. Situs inversus has stimulated the fanciful theory that it is due to twinning and that one of the mirror-image embryos has been resorbed in utero. Kartagener felt that the bronchiectasis was due to congenital deficiency of the supporting tissue of the bronchial wall, particularly since symptoms seemed to be present from the very beginning of life. Olsen pointed out that this is not always the case and postulated that a weakness of the bronchial wall with lack of the proper kind of elastic tissue could be the primary defect but that external factors were necessary for the development of clinical bronchiectasis (5). Subsequently many authors have reported from surgical or autopsy specimens that bronchiectasis found in Kartagener's syndrome can in no way be distinguished from "ordinary" or "acquired" bronchiectasis. The dilatation of bronchi can be cylindrical or saccular and show nonspecific chronic inflammatory changes (3, 9, 26, 27). In children with the typical clinical picture of the syndrome, bronchiectasis is not always demonstrable by bronchography (9, 28). In fact, bronchiectasis has never been demonstrated in a newborn child with Kartagener's syndrome. Facts of this nature have convinced most authors from about 1950 onwards that the bronchiectasis in Kartagener's syndrome is acquired. Kartagener himself partially altered his original view when he described "bronchiectasis of mixed etiology" and "endogenous nature" of the disease (3). It has been pointed out that the most characteristic lung affection in the syndrome is a generalized bronchitis rather than bronchiectasis (12).

Churchill believed that an altered secretory activity of the respiratory tract epithelium was responsible (29). Some authors have proposed an underlying atopic state (8, 11), but Holmes et al (16) found no evidence of hypersensitivity. These authors noted transient immunoglobulin deficiency during childhood in two subjects and there were occasional nonspecific changes in the thymus or in lymph nodes. Sharma found normal cell-mediated and humoral antibody responses in two siblings with the syndrome (30). Holmes et al pointed out that the condition affects the entire respiratory system and the respiratory epithelium in particular. However, on microscopic examination of the ciliated epithelium from the airways, they could find no pathognomonic changes. In the light of what we know today, these authors seem to have been on the right track.

Male Infertility

One of the arguments for the recessive inheritance of Kartagener's syndrome has been its nonoccurrence in the following generation. Remarkably little attention has been paid to the fact that males with the syndrome are usually infertile. There are occasional reports of men having children (15) but a review of the literature suggests that such cases are exceptional. Arge (31) presented two related families with 18 siblings, 16 of whom were married. Three males and one female had Kartagener's syndrome. All the married siblings including the affected female had offspring but not the three men with Kartagener's syndrome. The wife of one of the affected men was fertile in a previous marriage. Arge suggested that men with transposition of the viscera may be infertile or subfertile (31). Women do not seem to be infertile (15, 16, 18) and Kartagener originally described a woman who had borne a healthy child.

The male infertility associated with the syndrome has recently turned out to be of great theoretical interest. Indeed, the events leading to a new concept of the syndrome started with the observation in an infertility clinic of two brothers with living, metabolically normal spermatozoa, but with completely immobile sperm tails (32). Electron microscopy showed a characteristic defect in the sperm tails. There was a complete lack of the dynein arms of the outer microtubular doublets or filaments. The sperm tail is a modified flagellum or cilium. Its central portion, the axoneme, has two central microtubules surrounded by nine doublets, a 9 + 2 pattern. The outer filaments have projections called dynein arms which are thought to be responsible for the movements of the sperm tail. Sperm immotility has been explained as a genetic disorder involving production, assembly or attachment of the dynein arms (33).

One of the two patients observed in the infertility clinic had complete

Kartagener's syndrome and his brother had chronic airway infection. Since both patients had respiratory tract infections and since sperm tails are built in essentially the same way as cilia in other parts of the body, it seemed important to test ciliary function in their airways. The patient with Kartagener's syndrome and another subject who also had immotile sperm tails were investigated with respect to mucociliary transport in their lower airways (34). Interestingly enough, both subjects had an extremely slow and possibly absent mucociliary transport. This was also noted in the brother of the first Kartagener subject. Ciliated epithelium is present in the bronchi, nose, paranasal sinuses, nasopharynx and auditory tubes. It was suggested that the chronic or recurrent infection that occurs in subjects with complete or incomplete Kartagener's syndrome is caused by ciliary immotility in the lower and upper airways.

Ciliary Immotility Syndrome

It was assumed that cilia were congenitally immotile also in other ciliated epithelia of the human body, including embryonic cilia. Afzelius proposed that embryonic cilia might have an important function in determining the orientation of the viscera in the embryo (33, 34). The primitive gut, the archenteron tube, normally rotates to a dextral spiral, possibly guided by ciliary movements. With ciliary immotility, dextral and sinistral (to situs inversus) rotation would take place randomly. Thus, about half the affected subjects should have situs inversus, a finding seemingly supported in the above-reviewed literature.

Our material is now extended to seven subjects with chronic respiratory infections. Four of them have complete Kartageners syndrome and all have extremely slow mucociliary transport in the lungs. Dynein arms are lacking in sperm tails and cilia from nasal and bronchial mucosa, and respiratory cilia are also irregularly arranged. However, one of the subjects with immotile cilia and spermatozoa have dynein arms which indicates that the congenital ciliary immotility must not always be connected with this particular dynein arm deficiency. From a genetic point of view Kartagener's syndrome thus to some extent seems to be heterogenous (35).

The findings of immotile spermatozoa and cilia in Kartagener's syndrome have been confirmed by Pedersen et al (36, 37). These authors have also demonstrated a very slow mucociliary transport in the nose of a woman with the syndrome.

The practical consequence of these latest findings may be that in clinical analysis of cases with bronchiectasis the "ciliary immotility syndrome" should be considered. Since antibiotics have made bronchiectasis infrequent, its presence should henceforth raise the probability of this genetic disorder. The simplest investigation is sperm motility in the male or biopsy from the nasal or bronchial mucous membrane in the female.

Kartagener's syndrome has been a puzzling condition for doctors working in different fields; pulmonary medicine, internal medicine, pediatrics, otorhinolaryngology, and thoracic surgery. Now, more than 70 years after the first description and more than 40 years after Kartagener's first paper, a reasonable explanation of what underlies the condition seems to have been fashioned.

References

1. Kartagener M.: Zur Pathogenese der Bronchiektasien. I. Bronchiektasien bei Situs Viscerum Inversus. Klin Tuberk 83:489, 1933.
2. Siewert A.: Ueber einen Fall von Bronchiectasie bei einem Patienten mit Situs Inversus Viscerum. Klin Wochenschr (Berlin) 41:139, 1903.
3. Kartagener M., Stucki P.: Bronchiectasis with situs inversus. Arch Pediatr 79:193, 1962.
4. Adams R., Churchill E.: Situs inversus, sinusitis, bronchiectasis. J Thorac Surg 7:206, 1937.
5. Olsen A.: Bronchiectasis and dextrocardia. Am Rev Tub 47:435, 1943.
6. Lindskog G. E., Hubbel D.: An analysis of 215 cases of bronchiectasis. Surg Gynecol Obstet 100:643, 1955.
7. Cockayne E. A.: The genetics of transposition of the viscera. Q J Med 7:479, 1938.
8. Torgersen J.: Transposition of viscera-bronchiectasis and nasal polyps. Acta Radiol 28:17, 1947.
9. Bergstrom W. H., Cook C. D., Scannel J., Berenberg W.: Situs inversus, bronchiectasis and sinusitis. Pediatrics 6:573, 1950.
10. Overholt E. L., Bauman D. F.: Variants of Kartagener's syndrome in the same family. Ann Intern Med 48:574, 1958.
11. Safian L., Mandeville F.: Kartagener's syndrome in identical male twins and a female sibling. J Fla Med Assoc 45:1143, 1959.
12. Knox G., Murray S., Strang L.: A family with Kartagener's syndrome: linkage data. Ann Hum Genet 24:137, 1960.
13. Mayo P., Lexington K.: Kartagener's syndrome. J Thorac Cardiovasc Surg 42:39, 1961.
14. Cook C. D., Geller F., Hutchinson G. B., Gerald P., Allen E. H.: Blood grouping in three families with Kartegener's syndrome. Am J Hum Genet 14:290, 1962.
15. Logan W., Abbot O., Hatcher C.: Kartagener's triad. Dis Chest 48:613, 1965.
16. Holmes L. B., Blennerhassett J. B., Austen K. F.: A reappraisal of Kartagener's syndrome. Am J Med Sci 255:13, 1968.
17. Aarons G., Powell I.: The familial occurrence of the Kartagener triad in Jamaica. Postgrad Med J 45:736, 1969.
18. Katsuhara K., Kawamoto S., Wakabayashi T., Belsky J.: Situs inversus totalis and Kartagener's syndrome in a Japanese population. Chest 61:56, 1972.
19. Campell M.: The mode of inheritance in isolated laevocardia and dextrocardia and situs inversus. Br Heart J 25:803, 1963.
20. Miller D., Divertie M.: Kartagener's syndrome. Chest 62:130, 1972.
21. Divekar : Kartagener's syndrome. Indian J Med Sci 10:102, 1956.
22. Erasmus L. D.: Situs inversus viscerum and bronchiectasis. S Afr Med J 26:429, 1952.
23. Todd W., Yodaiken R.: A patient with Kartagener and Paterson-Brown-Kelly syndromes. JAMA 234:1248, 1975.
24. Burnell R., Robertson E.: Cystic fibrosis in a patient with Kartagener's syndrome. Am J Dis Child 127:746, 1974.
25. Amjad H., Richburg F., Adler E.: Kartagener's syndrome. Case report in an elderly man. JAMA 227:1420, 1974.
26. Taiana J., Villegas A., Schieppati E.: Kartagener's syndrome: report of a case treated by pulmonary resection. J Thorac Surg 30:34, 1954.
27. Kartagener M., Mülly K.: Bronchiektasien bei Situs viscerum inversus. Schweiz Z Tuberk 13:166, 1956.
28. Nichamin S.: Kartagener's syndrome in a newborn infant. JAMA 161:966, 1956.
29. Churchill E.: The segmental and lobar physiology and pathology of the lung. J Thorac Surg 18:279, 1949.

30. Sharma O.: Kartagener's syndrome. Immunologic studies. NY State J Med 72:1057, 1972.
31. Arge E.: Transposition of the viscera and sterility in men. Lancet 1:412, 1960.
32. Afzelius B. A., Eliasson R., Johnsen O., Lindholmer C.: Lack of dynein arms in immotile human spermatozoa. J Cell Biol 66:225, 1975.
33. Afzelius B.A.: A human syndrome caused by immotile cilia. Science 193:317, 1976.
34. Camner P., Mossberg B., Afzelius B.A.: Evidence for congenitally nonfunctioning cilia in the tracheobronchial tract in two subjects. Am Rev Respir Dis 112:807, 1975.
35. Eliasson R., Mossberg B., Camner P., Afzelius B. A.: A congenital ciliary abnormality as an etiological factor in chronic airway infections and male sterility. New Engl J Med 297:1, 1977.
36. Pedersen H., Rebbe H.: Absence of arms in the axoneme of immobile human spermatozoa. Biol Reprod 12:541, 1975.
37. Pedersen H., Mygind N.: Absence of axonemal arms in nasal mucosa cilia in Kartagener's syndrome. Nature 262:494, 1976.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Combination Chemotherapy (MACC) in Bronchogenic Carcinoma

A. PHILIPPE CHAHINIAN, JAMES F. HOLLAND, ALVIN S. TEIRSTEIN, AND PAUL A. KIRSCHNER

Bronchogenic carcinoma is a major challenge for oncologists. Its prognosis has not significantly improved in decades. Chemotherapy with single agents fails to prolong survival in most instances. Methotrexate, cyclophosphamide and adriamycin are among the most effective single agents with a response rate of approximately 20% each (1). CCNU (Lomustine) has the ability to cross the blood-brain barrier. In the present study, these four drugs have been combined together in an attempt to increase response rates and survival. Simultaneous use of cyclophosphamide with a nitrosourea or adriamycin has been found to be markedly synergistic in animal tumors (2). A detailed analysis on 41 patients with bronchogenic carcinoma has been published previously (2).

Material and Methods

Fifty-three patients with proven advanced bronchogenic carcinoma were treated with MACC therapy, including methotrexate (40mg/m^2 iv), adriamycin (40mg/m^2 iv), cyclophosphamide (400mg/m^2 iv) and CCNU (30mg/m^2 p.o.). All the drugs were given together on the same day and courses were repeated every 3 weeks provided that there was no residual toxicity. Mean age was 61 (range 36–76). There were 36 men and 17 women. Prior therapy included surgery (4 patients), radiotherapy (25 patients) and chemotherapy (2 patients). All patients had evidence of active and measurable disease at onset of therapy.

Results

Objective response (partial response >50%-PR- and complete response - CR) were seen in 24 patients (45%). Results by cell type were as follows:

Epidermoid	Adenocarcinoma	Small Cell	Large Cell	Undifferentiated
5PR/13	7PR/20	3CR + 6PR/10	1CR + 1PR/6	1PR/4

Response rate was highest for small cell (oat cell) carcinoma, but significant results were obtained in all other cell types. Overall response rate was 35% in non-small-cell carcinoma. There was a significant increase in survival between responders and non-responders.

Median duration of response was five months for squamous cell carcinoma, seven months for adenocarcinoma, and eight months for small cell carcinoma.

From the Departments of Neoplastic Diseases, Medicine (Pulmonary Division) and Thoracic Surgery, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

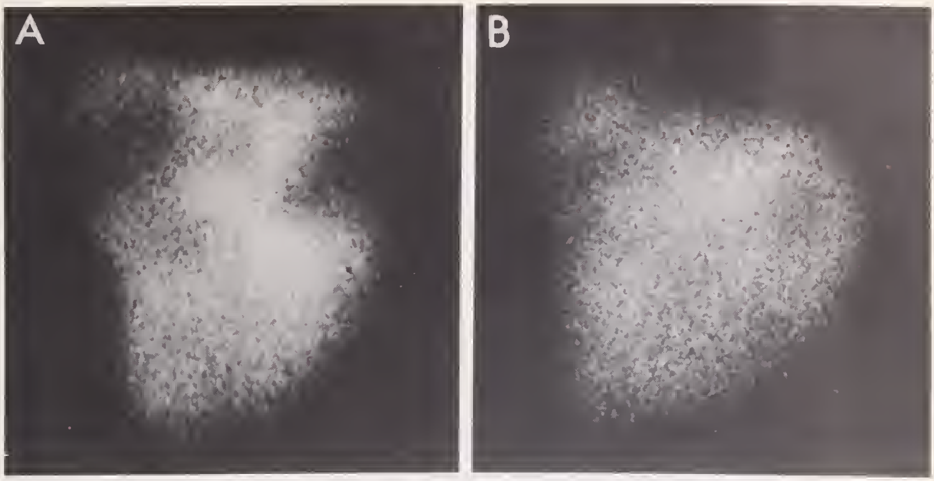

FIG. 1. Squamous cell carcinoma of the lung, metastatic to mediastinum, liver and bone. Right lateral view of liver scan (2.5 mCi of Tc99M sulfur colloid). *A* = before MACC; multiple focal defects; serum alkaline phosphatase = 189 mU/ml (normal <90), total bilirubin = 2.0 mg/100 ml (normal <1.0); *B* = after 5 cycles of MACC; partial response >50%; serum alkaline phosphatase = 96 mU/ml, total bilirubin = 0.3 mg/100 ml. Duration of response = 5 months. Survival = 9 months from onset of therapy.

These data are underestimated since most of the patients are still alive. Figures 1 and 2 (on next page) show some examples of response.

Toxicity was moderate and allowed for easy outpatient use. Nausea and alopecia were the most common. Bone marrow toxicity included leukopenia (<3000/cu mm), which occurred in 25 patients (47%), and thrombocytopenia (<100,000/cu mm) in 9 patients (17%). They occurred 10 to 14 days after the treatment and were reversible. Other toxic effects included stomatitis (11 cases), fever and/or sepsis (7 cases), nephrotoxicity (3 cases), skin rash (1 case). Cardiotoxicity occurred in one patient 4 months after completion of the total dose of adriamycin of 550mg/m^2. It was reversible. There was no drug-related death.

This is the only regimen of which we are aware that has significant activity in all types of bronchogenic carcinoma. It warrants further evaluation, particularly in an adjuvant setting after surgery, and the present authors have begun such studies.

References

1. Selawry, O. S.: On Chemotherapy of Lung Cancer: In *Lung Cancer Natural History, Prognosis and Therapy*. Edited by L. Israel and A. P. Chahinian. Academic Press, New York 1976, pp. 205–239.
2. Chahinian, A. P., Arnold, D. J., Cohen, J. M., Purpora, D. P., Jaffrey, I. S., Teirstein, A. S., Kirschner, P. A., and Holland, J. F.: Chemotherapy for Bronchogenic Carcinoma, JAMA 237:2392–2396, 1977.

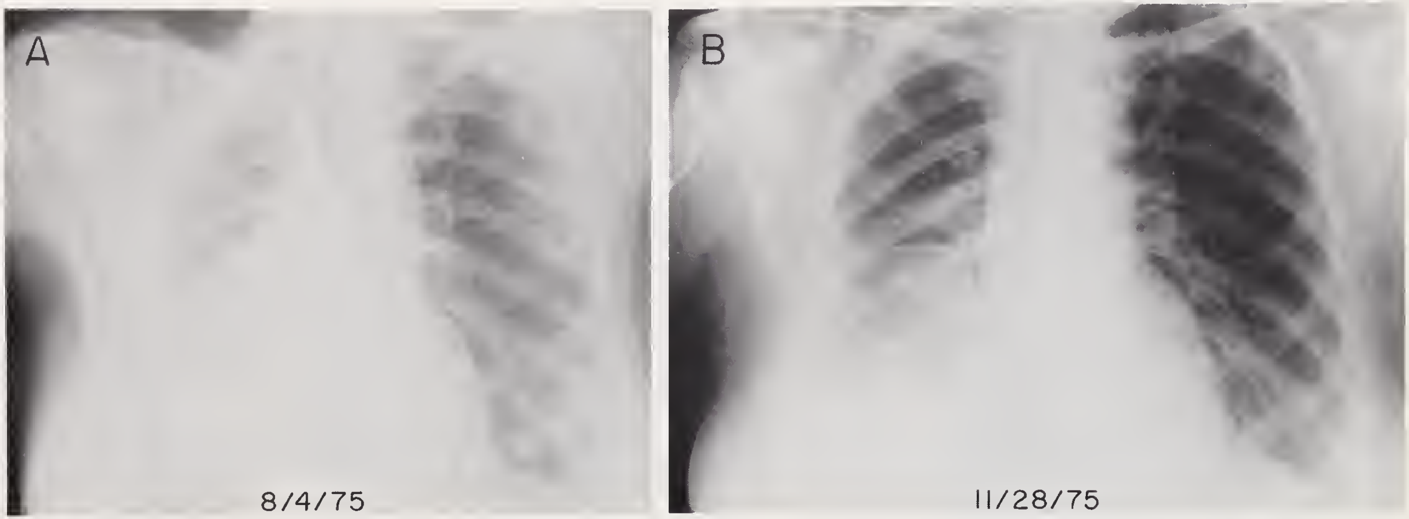

FIG. 2. Adenocarcinoma of the lung, metastatic to the right pleura, liver, and cervical nodes. Chest x-ray: *A* = before MACC, right pleural effusion; *B* = after 3 cycles of MACC, regression of effusion (without thoracentesis). Duration of response = 13 months; Survival = 14 months from onset of therapy.

The Mount Sinai Journal of Medicine
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

Fatal Intraalveolar and Interstitial Lung Fibrosis in Chlorambucil-Treated Chronic Lymphocytic Leukemia

OLAV REFVEM, M.D.

Case Report

S.B.AA., born in 1905, was a male clerk, who in 1932 had had a right-sided tuberculous pleuritis. In 1965 he had signs of incipient chronic lymphocytic leukemia (CLL), which during the following years progressed slowly. Since 1968 he has had troublesome sweating and loss of weight.

In January 1972, while in the hospital, his height was 174 cm, weight 67.5 kg, blood pressure 125/80 mm Hg. Peripheral and intraabdominal lymph nodes and the spleen were considerably enlarged. Hemoglobin was 11.8 g%, RBC 4,200,000, WBC 320,000, of which about 98% were lymphocytes, and platelets 160,000/mm^3. The bone marrow smear was dominated by lymphocytic cells. Serum total proteins and paper-electrophoretic fractions were normal; the BMR was + 64%, and thyroid function was normal. A chest radiograph showed thickening of the right pleura.

In February 1972 continuous chlorambucil treatment was started with 2 mg and gradually increased to 12.5 mg every morning. This was followed by general improvement. Chlorambucil was stopped in September 1972 when platelets had dropped to 60,000, WBC to 22,000, and hematocrit to 31%. In February, March and May 1973 local x-ray irradiation totaling 840 rads caused some decrease of the intraabdominal lymphnode masses and of the spleen. From August 1, 1973 chlorambucil, an average of 8.7 mg, and prednisolone 15–25 mg every morning had an excellent effect on his general condition. Because of thrombocytopenia (57,000) chlorambucil was stopped on September 13, whereas prednisolone 25 mg was continued; platelet counts soon reached 78,000. He was still able to work.

The last days of September he had a febrile airways infection. The fever reacted favorably to oxytetracycline 0.5 g three times a day and this medication was continued for a couple of weeks because of persistent cough and mucous expectoration.

On November 3 he had a fever of 39.7°C, with more cough and more mucus. Oxytetracycline once again had some clinical effect. On admission to hospital, November 6, his general condition was fair, the temperature subfebrile, and crepitant rales were heard over the base of the right lung. A chest radiograph showed partly confluent densities in the right lung's lower portions and also scattered finely patchy and reticular densities in the right upper lobe. In spite of antibiotics the temperature remained subfebrile for the first week, and thereafter irregularly febrile. There was moderate but persistent cough and

From the Medical Department A, Aker Hospital, Oslo 5, Norway.

scant mucous sputum; varying dyspnea. He was partially ambulant. Prednisolone was replaced by cortisone 25 mg four times a day. There was no suprarenal, renal, or cardiac insufficiency, but there was pulmonary incompetence with hypoxemia and hypocapnia. On November 12 a chest radiograph revealed a discrete reticular pattern (possibly interstitial edema) in most of the left lung also, and controls on November 16, 23 and 30 showed an inexorable and considerable progression bilaterally with only the left lung base remaining clear (See Fig. 1). He died on December 4, 1973.

Serum proteins were low, total 5.0–5.3 g%; albumin, 3.1–2.7 g%; and -globulins, 0.7 g%. Immune electrophoresis showed IgG 17%, IgA 15%, and IgM 73% of normal values; a small M-component of type IgG was present in the serum and the urine. Periodically there was slight proteinuria. ESR, 21–23 mm/1 hour; hemoglobin, 11.9–14.5 g%; hematocrit, 37–51%; WBC, 43,000–126,000, with more than 90% lymphocytes, platelets, 64,000–74,000. There

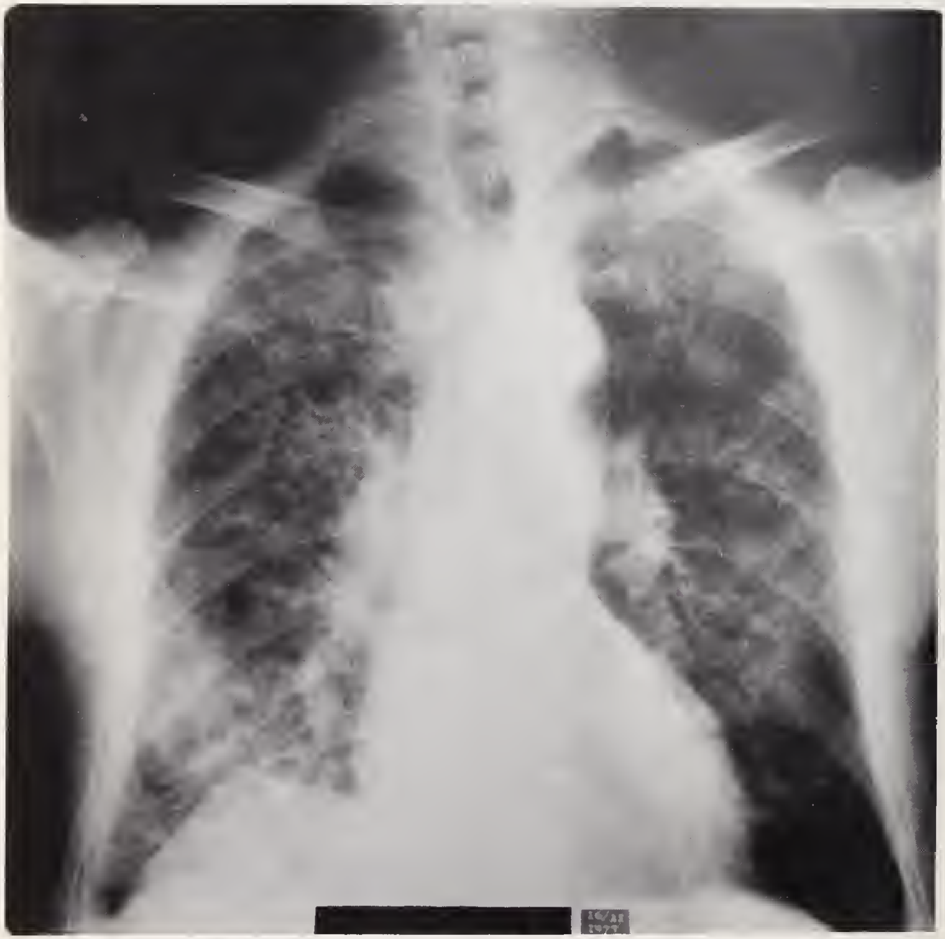

FIG. 1. Chest radiograph taken on November 16, 1973, showing bilateral patchy and reticular infiltration, with more confluent opacities at the right base.

was hypocalcemia (8.3–7.4 mg%) correspondent with the hypoproteinemia. Antistreptolysin and antistaphylolysin titres were normal; ANF and Coombs tests were negative. ECG was normal.

Diagnostic considerations

A pneumonia was the first-line responsibility to be met with. No pathogenic bacteria were recovered from the sputum, and the Mycoplasma pneumoniae CFT was negative. Tuberculosis with miliary spread was seriously considered in spite of a negative tuberculin test and negative search for tuberculosis by direct microscopy. In considering pulmonary mycosis, sputum cultures for fungi yielded moderate growth of Candida only, which could be due to contamination from the oral cavity. A suspicion of septicemia was not confirmed by 12 blood cultures for bacteria and fungi. A diffuse leukemic infiltration and lymphangitis carcinomatosa were also considered.

Treatment

The following drugs and remedies were tried without any traceable effect: oxytetracycline; trimetoprim-sulfametoxazol; erythromycin; penicillin, 30 million IU/day; cloxacillin; cefalotinsodium; streptomycin + isoniazid + myambutol; gammaglobulin; leucocyte-enriched blood; mucolytics; diuretics during the last week. Intermittent free oxygen had some effect on the dyspnea. *Autopsy findings* were those of Chronic lymphocytic leukemia. Suprarenal glands and heart were without overt abnormalities. The lungs were large and heavy, 2000 g, their consistency firm and tough, with diffuse infiltrates palpable in all lobes. The parenchyma was grey-red and on pressure yielded a small amount of edematous fluid. Histologic studies (K. A. Larsen) showed scattered lymphocyte accumulations, mostly in the interstitia, like those found in other parenchymatous organs. A diffusely dominating feature of varying severity was an abundant and partially fibrinous exudate that in many alveoli showed organization and reticular fibrosis. The alveolar epithelium was intact only in air-filled alveoli. Most alveoli had no or scant lining epithelium and contained degenerated epithelium, macrophages, and probably type II pneumocytes and scattered inflammatory cells; there were no eosinophils. There also was some interstitial fibrosis with reticular and collagen fibrils (Fig. 2). Pneumocystis carinii or other causative agents could not be seen. Sputum cultures for tuberculosis were all negative.

Discussion

What was the cause of the fatal diffuse lung disorder, characterized mainly by alveolar epitheliolysis, exudation and intraalveolar fibrosis? The histologic picture seems identical to that sometime following treatment with busulphan, methotrexate and bleomycin (1, 2), in which cough, dyspnea and fever are also clinical characteristics. Until now the author has succeeded in tracing only one detailed report (3) incriminating chlorambucil; the histologic findings were those of diffuse interstitial, not intraalveolar, pulmonary fibro-

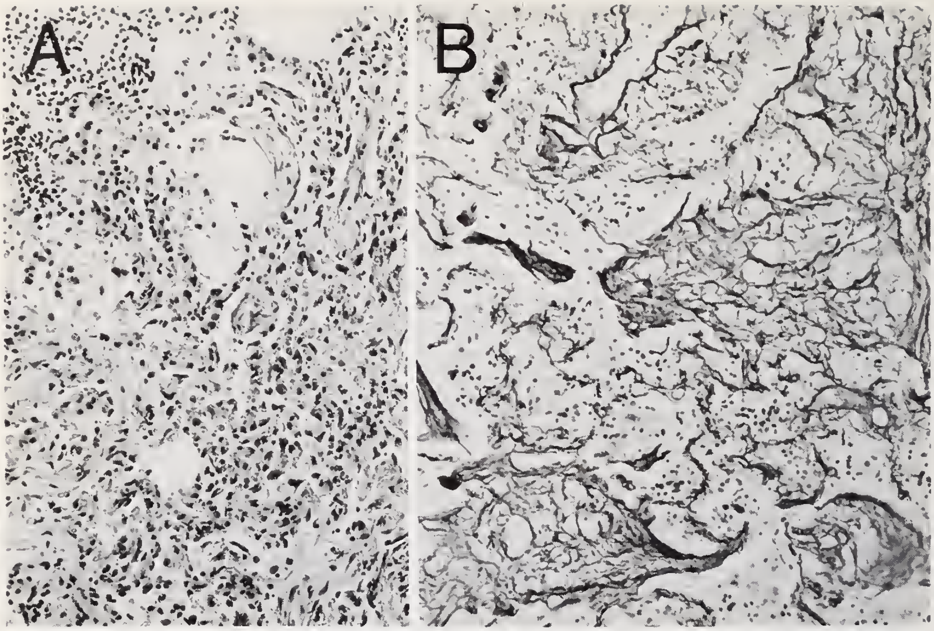

FIG. 2. A. In the alveoli, desquamated epithelium together with many macrophages. In and about the alveoli are a good deal of inflammatory cells, including lymphocytic infiltrates (CLL). Scattered intraalveolar reticular fibrosis and some interstitial fibrosis (Hematoxylin and eosin × 160). B. Extensive intraalveolar fibrosis resulting from organization of proteinaceous exudate, and some interstitial fibrosis (Silver-impregnation × 60).

sis. Crofton and Douglas (4) in their book briefly mention having seen a case following chlorambucil and apparently responding rapidly to corticosteroids.

Our patient's Chronic lymphocytic leukemia (CLL) was untreated until from February 1972 chlorambucil was administered every day for 9 months. A second course of 6 weeks was given from August 1, 1973. The total dose (2.13 + 0.36 g) approximated 2.5 g. From the clinical and hematologic point of view the chlorambucil treatment, although prolonged and relatively heavy, seemed adequate. The clinical debut of his lung disorder seems to be at the end of September 1973, i.e., two weeks after stopping treatment since, from then on, cough and scant mucoid sputum was a constant and dominant feature until death. The shortlived febrile episodes preceding admission may well have been intercurrent infections. It is known that early stages of the pneumopathy following oncolytics may not be visible radiologically, and that rapid febrile progression may take place even after the drug has been stopped. In our case corticosteroids seemed of no use in counteracting the development.

On the other hand, there can be no doubt that cytostatic and corticosteroid treatment in this CLL patient with severe hypogammaglobulinemia, had rendered him rather defenseless even to opportunistic infectious agents. Even if not demonstrated, an infection cannot entirely be ruled out as the only cause—or a contributory cause—of his generalized lung disorder, especially since it seems established that, exceptionally, similar changes can be caused by certain viruses, by Mycoplasma pneumoniae and by Pneumocystis carinii.

The close analogue to other alkylating agents, such as busulphan, however, makes a chlorambucil-induced pneumonitis sufficiently probable to oblige the clinician to be on the lookout for this complication, preferably in an early and possibly reversible phase. The diagnosis will have to be established by lung biopsy.

References

1. Rosenow, E. C.: The Spectrum of Drug-Induced Pulmonary Disease (Review), Ann Intern Med 77:977, 1972.
2. Gutin, P. H., Green, M. R., Bleyer, W. A., Bauer, V. L., Wiernik, P. H., and Walker, M. D.: Methotrexate Pneumonitis Induced by Intrathecal Methotrexate Therapy, Cancer 38:1529, 1976.
3. Jacobs, S. (ed): The Hamman-Rich Syndrome following Treatment of Lymphoma with Chlorambucil, J La State Med Soc 127:311, 1975.
4. Crofton, J. and Douglas, A. (eds): *Respiratory Diseases*. 2d. edition, Blackwell Scientific Publications, Oxford, London, Edinburgh, Melbourne 1975, p. 613.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

The Sequence of Physiologic Changes in Pulmonary Sarcoidosis: Correlation with Radiographic Stages and Response to Therapy*

ALBERT MILLER, M.D., ALVIN S. TEIRSTEIN, M.D., AND MING T. CHUANG, M.D.

Previous studies in our laboratory have shown a relationship between physiologic abnormalities and radiographic findings in sarcoidosis (1, 2). At this time, it is appropriate to attempt to answer several pertinent questions:

1. Is there a sequence of altered pulmonary function in sarcoidosis which correlates with the underlying pathologic changes?
2. Do these physiologic patterns correlate with the widely used radiographic stages established by Dr. Siltzbach? (3). Do changes in pulmonary function provide another basis for staging pulmonary involvement? Do they provide significant additional information which may not be apparent from radiographic and clinical findings?
3. What effect does corticosteroid therapy have on lung function as compared with clinical and radiographic response? Can physiologic measurements provide more precise information on when to intervene therapeutically to prevent the cardiorespiratory failure which befalls a small seqment of patients with sarcoidosis?

1. *The evolution of pulmonary function changes in sarcoidosis*

The several stages seen in sarcoidosis patients, the tendency to radiographic resolution in many patients while some develop fibrosis, and the variable effects of therapy on radiographic appearance and lung function have obscured the relationship between stage of disease and functional impairment. In several published studies, no attempt was made to analyze physiologic changes according to stage of disease; in others, not all stages of pulmonary sarcoidosis were adequately represented.

To correlate physiologic changes with clinical staging, we selected for study 60 patients with clearcut radiographic abnormalities falling into 3 categories: Stage I (hilar lymphadenopathy alone), 25; Stage II (lymphadenopathy plus streaky, nodular or pneumonic parenchymal infiltrates), 19; and Fibrosis (a subgroup of Stage III with the most long-standing radiographic changes, who show hilar or diaphragmatic elevation, tracheal deviation and/or bullae), 16. The diagnosis of sarcoidosis was histologically confirmed in all cases by biopsy and/or the Kveim-Siltzbach test. A number of patients whose radiographic appearance was not typical of one of the above categories were not included in this study.

From the Pulmonary Laboratory and Sarcoidosis Clinic, Pulmonary Division, Department of Medicine, The Mount Sinai Hospital, New York, N.Y. 10029.

* This work was supported in part by the Jack Martin Fund.

As seen in Table I, mean vital capacity (VC), expressed as percent of predicted value, fell as the stage of disease advanced. Differences between each stage were significant ($p \leq 0.05$). Similar differences were observed for maximum voluntary ventilation (MVV) and forced expiratory flow over the mid-VC (FEF_{25-75}), both expressed as percent of predicted values, and for the nitrogen gradient after the single-breath inhalation of 100% oxygen. Differences in volume-specific flow rates (FEF_{25-75}/FVC; FEV_1/FVC; FEF_{50}/FVC; and FEF_{75}/FVC) were found only for the patients with fibrosis. Percent predicted difusing capacity (D_LCO_{SB}) also fell with each successive stage, although statistical significance was demonstrated only between the first and last stages.

Of all the measurements in Stage I, only the mean value for D_LCO_{SB} was abnormal, whereas in Stage II, the mean value for VC was abnormal as well. The mean values for all tests were abnormal when fibrosis was present. Despite evidence of airway obstruction in the patients with fibrosis, residual volume and total lung capacity were not elevated (1).

As seen in Table II, arterial oxygen tensions fell with progressive stage of disease. Differences were not statistically significant at rest but were highly so after exercise. In Stage I patients, paO_2 rose with exercise as it does in

TABLE I

Mean Values for Pulmonary Function Tests in Various Stages of Sarcoidosis

	Stage I (25)*	Stage II (19)*	Fibrosis (16)*
Age (years)	33.6	35.5**	43.8
Vital Capacity (% pred)	87.9	72.5	59.4
Maximum Voluntary Ventilation (% pred)	117.1	92.6	64.7
Forced Expiratory Flow 25–75% (% pred)	88.6	67.1	39.8
Forced Expiratory Volume-1 sec/FVC	79.9	78.4	70.4
Forced Expiratory Flow 50/FVC	1.17	0.96	0.65
Forced Expiratory Flow 75/FVC	0.40	0.36	0.27
N_2 Gradient (%)	0.86	1.48	4.9
Diffusing Capacity for CO (SB) (% pred)	72.7	62.0	57.3

* Number of patients in each group

** Underlined values are significantly different, $p \leq 0.05$.

TABLE II

Arterial Blood Gases (Mean Values) in Various Stages of Sarcoidosis

	Stage I (15)*	Stage II (12)*	Fibrosis (6)*
Rest	84.9	78.0	71.8
PaO_2 mmHg			
Exercise	88.1**	71.1	61.2
$PaCO_2$ mmHg	37.5	38.9	36.7
pH	7.412	7.411	7.372

* Number of patients in each group

** Underlined values are significantly different normal subjects. In the other two groups (Stage II and subgroup Stage III), paO_2 fell with exercise, consistent with loss of diffusion surface or alteration in diffusion pathway.

Decrease in mean values for the various measurements of lung function was paralleled by increase in prevalence of abnormality with advancing stage of disease (Table III). The VC was abnormal in 20% of patients in Stage I, 63% of those in Stage II, and 88% of patients with fibrosis. Patients in Stages I and II had a relatively low prevalence of impairment of air flow (corrected for volume), whereas this abnormality was present in 69% to 81% of patients with fibrosis, depending on the flow rate used.

Impairment in patients with hilar node involvement as the only radiographic abnormality was not generally evident from study of lung volumes, conventional measurements of air flow or airway resistance (2). In this group, 20% showed a decrease in FEV_1/FVC; and 20% showed a reduction in lung volumes (generally in VC), whereas 55% had a diminished D_LCO_{SB}. In Stage II, 63% had a decreased VC and 92% a diminished D_L. When fibrosis was present, VC was abnormal in 88% and overt airway obstruction ($FEV_1/FVC \leq 0.74$) was detected in 69%.

These findings indicate that the degree and the prevalence of impairment in pulmonary sarcoidosis increase with progressive radiographic change and that a different functional pattern could be considered characteristic of each stage. Thus, in Stage I impaired gas transfer, either by itself or with small airway obstruction, is typical. In the later stages, the diffusion defect worsens and is usually associated with restriction in Stage II and combined restrictive-obstructive impairment when fibrosis is present.

These abnormal patterns are concordant with the pathologic changes in the three stages of pulmonary sarcoidosis. Although not evident on radiographic examination, cellular interstitial infiltrates and parenchymal granulomas are almost universally present in Stage I (4, 5). These lesions would be expected to manifest their presence by diminution in gas transfer. As the infiltrates and granulomas enlarge and coalesce, and as focal fibrosis takes place (still not obvious on radiographic examiniation), lung volumes are reduced and gas transfer suffers further. At this stage (Stage II), paO_2 falls

TABLE III

Prevalence of Pulmonary Function Impairment in Various Stages of Sarcoidosis

		Stage I	Stage II	Fibrosis
Vital Capacity*	≤79%	5/25 (20%)	12/19 (63%)	14/16 (88%)
Forced Expiratory Volume-1 sec/FVC	≤0.74	5/25 (20%)	4/19 (21%)	11/16 (69%)
Forced Expiratory Flow 25–75%*	≤67%	7/25 (28%)	9/19 (47%)	14/16 (88%)
Forced Expiratory Flow 50/FVC	≤0.69	0/20 (0%)	3/13 (23%)	12/16 (75%)
Forced Expiratory Flow 75/FVC	≤0.29	7/20 (35%)	5/13 (38%)	13/16 (81%)
Diffusing Capacity for CO (SB)*	≤75%	12/22 (55%)	11/12 (92%)	6/6 (100%)
Exercise paO_2	≤1 SD below normal (2)	4/15 (27%)	10/12 (83%)	6/6 (100%)

* Percent of predicted value

** Underlined values are significantly different with exercise. In the late stage, as sarcoidal granulomas become hyalinized, their characteristic localization around the airways (6, 7) results in peribronchial and peribronchiolar fibrosis and obstruction to airflow becomes manifest. The gross fibrosis present in long-standing and extensive disease results in marked shrinkage in lung volumes and distortion of the bronchi, further impairing air flow.

2. *Comparison of Functional and Radiographic Assessments of Pulmonary Involvement*

Despite the correlation between radiographic staging and physiologic change demonstrated for many patients with sarcoidosis, there are a significant number for whom precise radiographic staging is difficult or physiologic alterations are clearly inconsistent with radiographic appearance. In these, the physiologic changes may better reflect the extent and severity of pulmonary involvement.

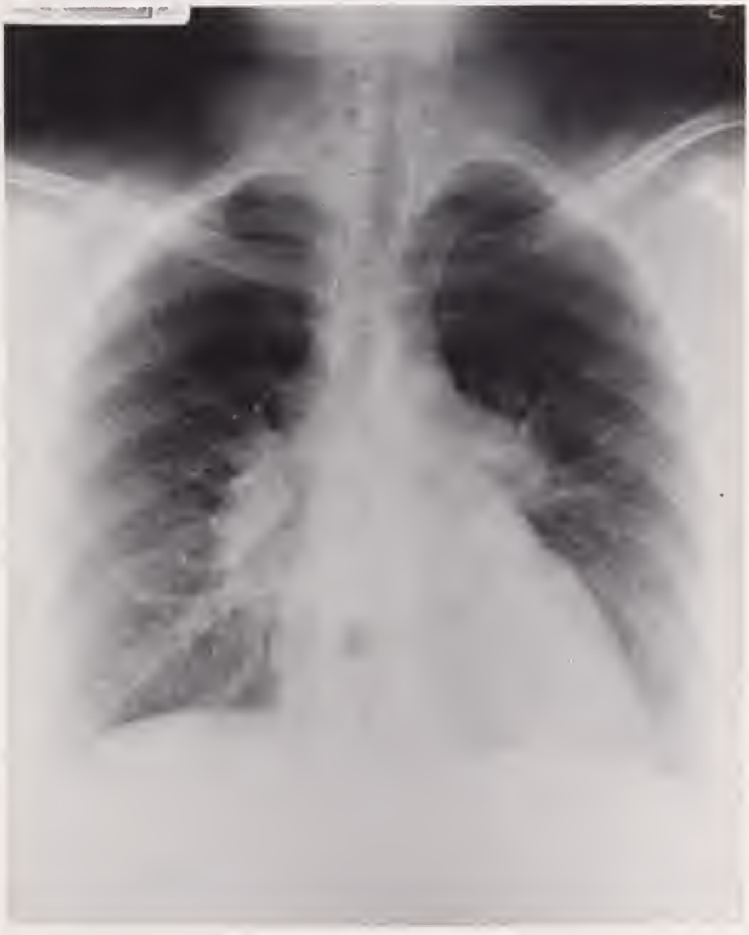

FIG. 1. Chest film (PA view) of a 39-year-old nonsmoking black woman showing hilar adenopathy and normal lung fields despite severe functional impairment (Table IV).

Especially for patients in whom fibrosis results in radiographically evident distortion and displacement of hila, trachea or diaphragm, physiologic tests may provide useful additional data. On the one hand, the marked decrease in vital capacity, total lung capacity and diffusion in this group parallels the

TABLE IV

Pulmonary Function in a 39-Year-Old Nonsmoker with "Stage I" Sarcoidosis

Vital Capacity	2680 cc	(65%)*
Forced Expiratory Volume-1 sec/FVC	0.39	
Forced Expiratory Flow 25–75%	0.44 L/sec	(13%)*
Mid-expiratory Time	3.1 sec	
Forced Expiratory Flow 75/FVC	0.06	
Maximum Voluntary Ventilation	32 L/min	(29%)*
Diffusing Capacity for CO (SB)	17.5 cc/min/mmHg	(64%)*

* Percent of predicted value

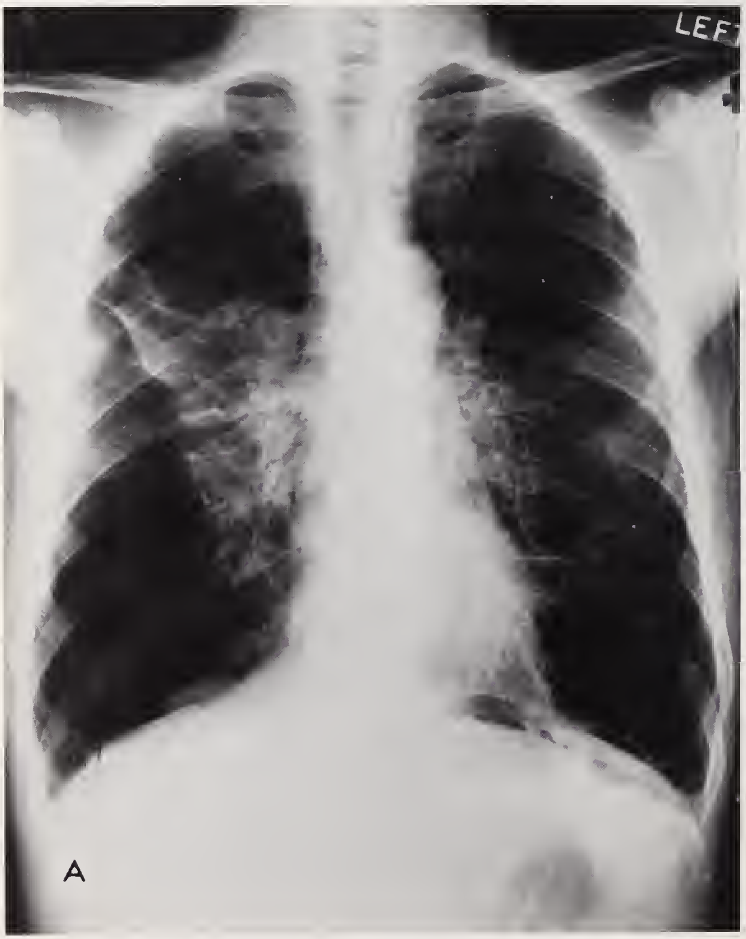

FIG. 2A

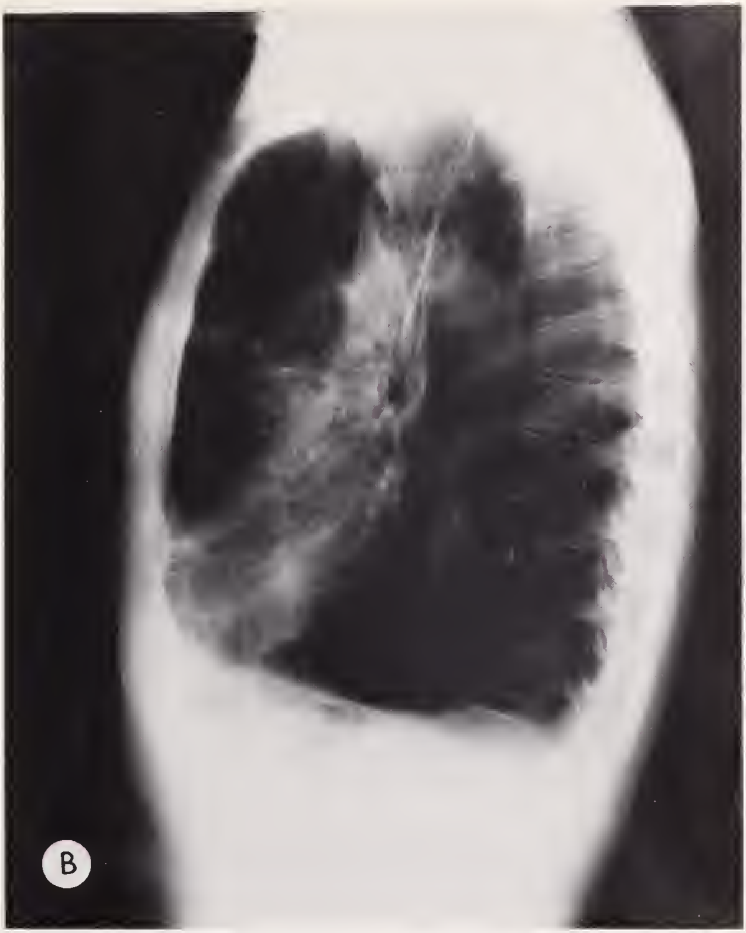

FIG. 2(A and B). Chest films (PA and lateral views) of a 65-year-old white male smoker with typical "bullous emphysema" (Table V).

fibrotic contraction of lung and elevation of the diaphragm seen on the x-ray film. On the other hand, the severity and frequency of airway obstruction would not be suspected on radiographic examination. Except for bullae, these patients with long-standing sarcoidosis show none of the radiographic hallmarks of airway obstruction seen in patients with nonsarcoidal chronic airway obstruction. We have come to regard the physiologic demonstration of irreversible airway obstruction in a patient with sarcoidosis (especially a nonsmoker) as evidence for the presence of fibrosis and generally, for chronicity of disease, whether or not compatible changes are visible on the chest film. Figure 1 shows the characteristic Stage I radiographic appearance of such a patient, a 39-year-old nonsmoking black woman. Her severe combined obstructive-restrictive impairment, recorded in Table IV, strongly suggests more longstanding and extensive pulmonary involvment that does her chest roentgenogram.

Because we have found severe airway obstruction and bulla formation to be common in late pulmonary sarcoidosis, we have investigated patients with typical bullous emphysema in whom sarcoidosis had not been suspected. Several have shown evidence of sarcoidosis on histologic examination. This is illustrated by the following case, a 65-year-old man (8) with incapacitating shortness of breath before he underwent bilateral thoracotomy for multiple bullectomies and pleurodesis. His chest films are seen in Figure 2. The diagnosis of bullous emphysema was confirmed by the demonstration on pulmonary function testing (Table V) of marked air trapping (the difference between functional residual capacity by plethysmography and by helium dilution was 2.5 L), as well as severe airway obstruction. Histologic examination of tissue obtained at surgery revealed many noncaseating granulomas in the lung and mediastinal lymph nodes.

In addition to patients who had bullous emphysema and were found to have histologic evidence of sarcoidosis, we have followed patients through the classic stages of pulmonary sarcoidosis to an end-stage with the clinical, physiologic and radiographic picture of bullous emphysema. Had they not been observed from the earlier stages of their disease onward, sarcoidosis would not have been considered likely as the underlying diagnosis.

In sarcoidosis, airway obstruction may be present in the early stages as well. Patients with dated, early disease may show evidence of "small airway" involvement, which probably results from deposition of granulomas in bronchiolar and peribronchiolar tissues. These granulomas may sometimes be seen bulging into and occluding the lumen (6). In one of our studies (1), reduction in air flow at low lung volume with normal FEV_1/FVC suggested the presence of small airway obstruction in 6 of 25 patients (24%) with Stage I sarcoidosis who did not give a history of smoking, asthma or occupational exposure. In 4 of these 6, it was the only abnormality in the maximum expiratory flow-volume curve; in 2, the VC was reduced as well. Other investigators have confirmed small airway obstruction in Stage I sarcoidosis

TABLE V

Pulmonary Function in a 65-Year-Old Smoker with "Bullous Emphysema" and Noncaseating Granulomas of Lung and Mediastinal Nodes

Vital Capacity	1220 cc (31%)*
Functional Residual Capacity-Helium	2850 cc
Functional Residual Capacity-Plethysmography	5430 cc
"Trapped Gas"	2580 cc
Residual Volume	4790 cc (184%)*
Total Lung Capacity	6010 cc (91%)*
RV/TLC	0.80
Maximum Voluntary Ventilation	25 L/min (31%)*
Forced Expiratory Volume-1 sec/FVC	0.40
Forced Expiratory Flow 25–75%	0.2 L/sec (8%)*
Forced Expiratory Flow 75/FVC	0.04
Arterial 0_2 tension (resting)	41 mmHg
Arterial CO_2 tension	51 mmHg

* Percent of predicted value

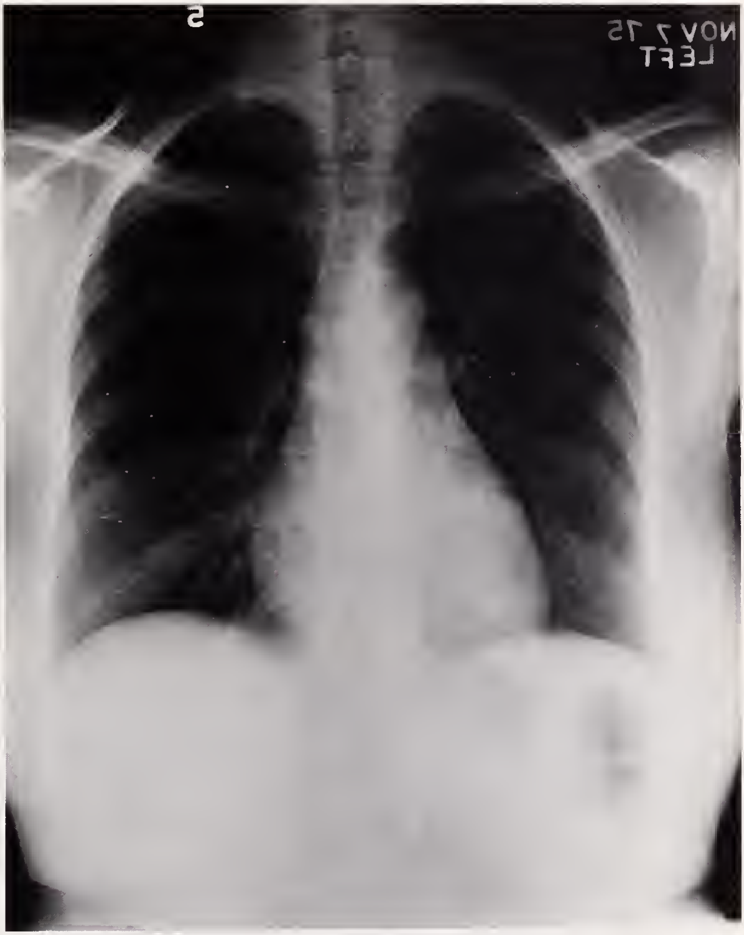

FIG. 3. Normal chest film (PA view) of a 40-year-old nonsmoking black woman with severe defect in gas transfer (Table VI).

by finding an increased closing volume (9) and increased upstream resistance with normal conductance in the large airways (10).

The patient with sarcoidosis who has a normal chest x-ray is an excellent example of the discordance between functional status and radiographic appearance (11). This disparity is illustrated by a 40-year-old nonsmoking woman with a positive Kveim-Siltzbach test, whose normal chest film (Fig. 3) gives no hint of a severe diminution in diffusing capacity and exercise paO_2 (Table VI). Diffusing capacity is the most consistently abnormal test in all patients with sarcoidosis including those with a normal chest x-ray (11). A normal chest x-ray generally results when lesions have run their course. However, radiographically inapparent residual inflammation, granulomas and/or fibrosis may be strategically placed in the alveolar-capillary membrane, causing impaired diffusion or, in and around bronchi and bronchioles, causing airway obstruction.

TABLE VI

Pulmonary Function in a 40-Year-Old Nonsmoker with a Normal Chest X-Ray and Positive Kveim Test

Vital Capacity	2750 cc	(80%)*
Forced Expiratory Volume-1 sec/FVC	0.91	
Forced Expiratory Flow 25–75%	3.2 L/sec	(102%)*
Mid-expiratory Time	0.38 sec	
Forced Expiratory Flow 75/FVC	0.67	
Maximum Voluntary Ventilation	74 L/min	(88%)*
Diffusing Capacity for CO (SB)	9.8 cc/min/mmHg	(47%)*
Arterial O_2 Tension (rest → exercise)	72 → 59 mmHg	

* Percent of predicted value

3. *Pulmonary Function Response to Corticosteroid Therapy*

General experience has been that clinical wellbeing and radiographic clearing precede and surpass improvement in pulmonary function when corticosteroids are used to treat pulmonary sarcoidosis (12). Lack of improvement in pulmonary function may indicate that irreversible lesions were already present before treatment was instituted.

Several authors (12–14) have suggested that corticosteroid therapy is only palliative and does not alter the long-term outcome. This contention is based on experiences in which the duration of treatment has been short (3–6 months) and/or the dosage suboptimal. Current recommendations of the Subcommittee on Therapy of the International Committee on Sarcoidosis are for initial dosage levels of 30–40 mg prednisone daily for a span of one to two years (15). Treatment is reinstituted for a similar period of time in the event of relapse (16, 17). Corticosteroids should be employed in disseminated disease if lung function is significantly impaired or if radiographic remission has not taken place in 6 to 12 months of observation (18). Alternate day dosage has been advocated (18) but may not be applicable to seriously ill patients (16).

Numerous studies have demonstrated improvement in lung function with corticosteroids, ranging from reversal of exercise hyperventilation (19) to improvement in lung mechanics (20). Vital capacity improves more frequently than does D_L, which rarely returns to normal levels regardless of radiographic or clinical improvement (16, 20). Sharma et al related a beneficial response in lung function to severity of impairment (21). All patients with severe impairment ($D_L < 65$ percent of predicted) improved with treatment, even if the radiographic appearance of the lungs did not, whereas improvement in function was uncommon in the untreated group despite radiographic resolution. In a recent follow-up of the same group of patients studied by Sharma et al, Colp (22) also noted that treatment brought about significant functional improvement in those with severe impairment, even when the disease was extensive and of long standing, and did not clear radiologically. On the other hand, most untreated patients showed no increase in vital capacity and slight further decrease in D_L. Major worsening of lung function was observed in 10% of the untreated group.

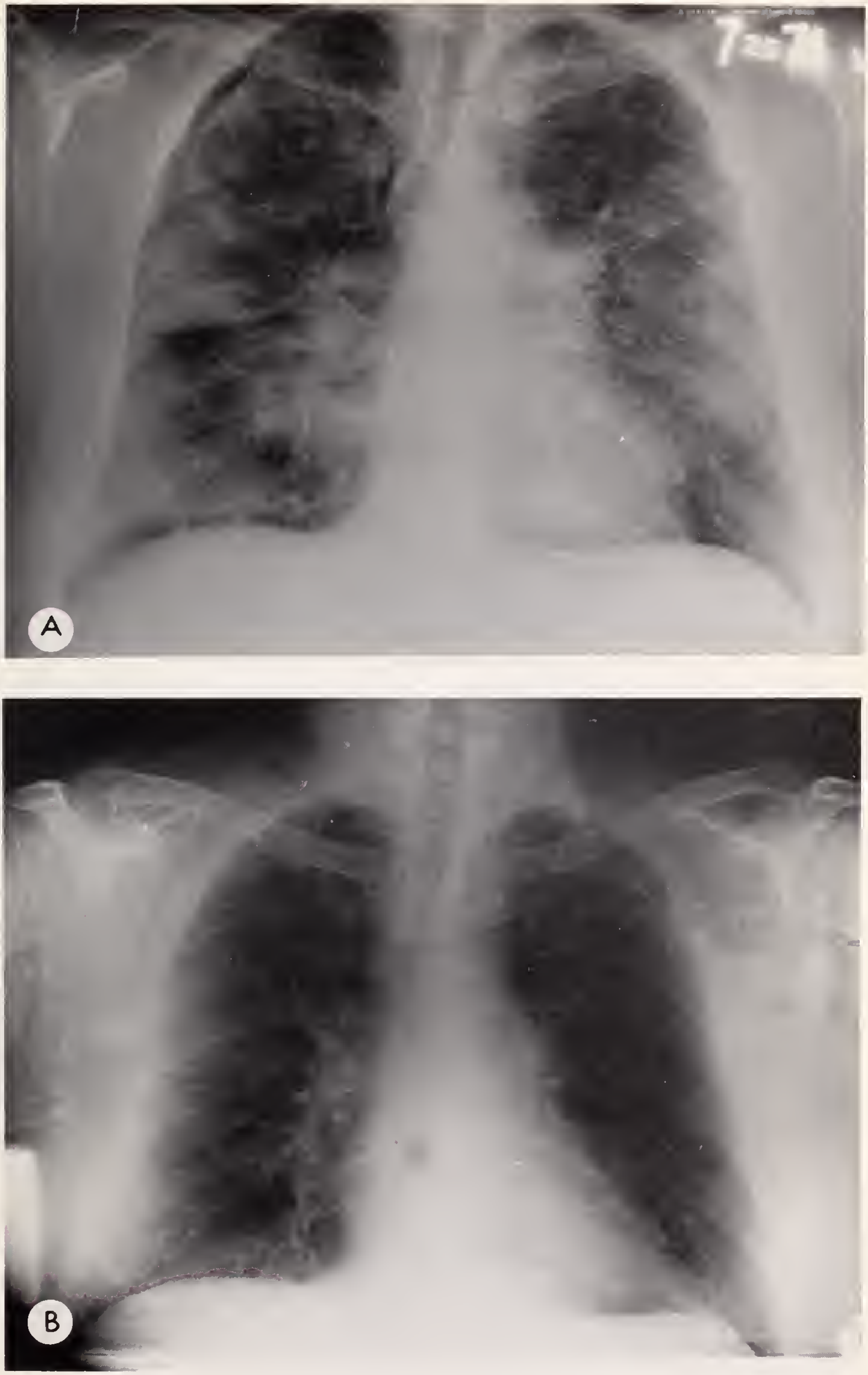

FIG. 4. Chest films (PA views) of a 30-year-old white male smoker. 4A shows extensive confluent micronodular infiltration, and a small pneumothorax on the right side which followed transbronchial biopsy. 4B after 3 weeks of corticosteroid therapy, shows striking resolution of the infiltrates (Table VII).

Many of the effects of corticosteroids on lung function in sarcoidosis are illustrated by the following case. The patient is a 33-year-old obese white man who has continued to smoke two packages of cigarettes a day. Kveim-Siltzbach test and transbronchial biopsy were both positive. Despite the striking radiographic appearance (Fig. 4A), which Dr. Siltzbach aptly terms "farina lung," the patient was free of symptoms when first seen in July of 1974. Impairment of lung volumes and gas exchange was minimal (Table VII) and he was not treated. Four months later, his symptomatic status and radiographic appearance remained unchanged but gas exchange had markedly deteriorated, with a fall in D_LCO_{SB} and exercise paO_2. It is agreed that patients with mild functional impairment, as exhibited by this patient on his first study, should be carefully followed with serial testing (22). Had this not been done, the deterioration in pulmonary function would not have been appreciated. Functional deterioration in untreated patients, which often occurs within two years of the onset of their sarcoidosis (20), is a generally accepted indication for therapy (15, 20, 22).

Three weeks after prednisone (30 mg/day) was instituted, the chest film showed marked clearing (Fig. 4B), which has been sustained. Six months after starting treatment, vital capacity had increased 450 cc and total lung capacity 1450 cc, but D_LCO and exercise paO_2 were not increased. Only after eighteen months of therapy did these measurements begin to improve. This patient exhibits a typical response to treatment in that the vital capacity improved earlier than did the D_L or exercise paO_2. If therapy had not been continued for as long as eighteen months, this improvement in gas exchange might not have occurred. The patient's airway obstruction, which was unresponsive to bronchodilator aerosols, never improved. It is probable that his airway obstruction is caused by the sarcoidosis, since its severity exceeds the degree of obstruction expected from smoking in such a young man.

The improvement in gas exchange, which has been maintained on reduced steroid dosage, may forestall the development of cor pulmonale in the patient under discussion. In an investigation of the pulmonary circulation in sarcoidosis, Emirgil et al (23) found that increased pulmonary vascular resistance, increased pulmonary artery pressure, and reduced cardiac index all correlated with impairment in diffusing capacity. When D_LCO was 40 percent of predicted, right-sided cardiodynamic abnormalities were uniformly present (23).

Summary

We have demonstrated that for many patients with pulmonary sarcoidosis, there is a sequence of pulmonary function changes which correlates with the histologic evolution of the disease and with the radiographic stages. The stage of hilar adenopathy (I) is typically associated with impaired diffusion, the stage of parenchymal involvement (II) with the advent of restriction in lung volumes and that of fibrosis (late Stage III) with the advent of overt airway obstruction.

When physiologic alterations are inconsistent with the radiographic ap-

TABLE VII

Pulmonary Function Response to Steroid Therapy in a 30-Year-Old White Male with Sarcoidosis

	7/23/74	11/21/74		5/23/75	4/13/76	1/27/77
Vital Capacity (cc)	3810 (75%)*	3650 (72%)	Corticosteroid Rx	4100 (81%)	4010 (82%)	4100 (85%)
Residual Volume (cc)	1440 (76%)	–		2600 (137%)	–	3490 (191%)
Total Lung Capacity (cc)	5250 (75%)	–		6700 (96%)	–	7590 (114%)
Forced Expiratory Volume-1 sec/FVC	0.63	0.61		0.60	0.58	0.58
Forced Expiratory Flow 25–75 (L/sec)	1.3 (31%)	1.0 (23%)		1.3 (31%)	1.2 (27%)	1.1 (27%)
Forced Expiratory Flow 75/FVC	–	–		0.10	0.1	0.10
Maximum Voluntary Ventilation (L/min)	118 (81%)	128 (88%)		144 (92%)	131 (87%)	110 (73%)
Diffusing Capacity for CO (SB) (cc/min/mmHg)	22.2 (70%)	13.0 (40%)		13.7 (43%)	17.7 (59%)	18.5 (63%)
PaO_2 (rest → exercise; mmHg)	69 → 68	66 → 59		78 → 56		74 → 68**

* Percent of predicted value

** Repeated: 83 → 77

pearance, they may more accurately reflect the extent and severity of pulmonary involvement. As examples, severe decrease in diffusion may be present with a normal lung field and restrictive-obstructive impairment may indicate a degree of fibrosis which is not recognized from the chest film.

Significant impairment of lung function, whether demonstrated on first study of the patient or on frequent follow-up measurements, is an indication for treatment. Corticosteroids in adequate dosage bring about improvement in lung function which often lags behind symptomatic and radiographic resolution. Improvement in lung mechanics, easily demonstrated by measuring the vital capacity, is a consistent result of therapy. Increase in D_LCO or exercise paO_2 often requires a prolonged course of treatment (about 2 years). Improvement in gas exchange may help to avert cor pulmonale.

References

1. Miller, A., Teirstein, A. S., Jackler, I., Chuang, M., and Siltzbach, L. E.: Airway Function in Chronic Pulmonary Sarcoidosis with Fibrosis, Am Rev Resp Dis 109:179, 1974.
2. Miller, A., Chuang, M., Teirstein, A. S., and Siltzbach, L. E.: Pulmonary Function in Stage I and II Pulmonary Sarcoidosis, Ann NY Acad Sci 289:292, 1976.
3. Siltzbach, L. E.: Sarcoidosis: Clinical Features and Management, Med Clinics N Am 51:483, 1967.
4. Eule, H.: Findings by Lung Biopsy in Patients with Lofgren's Syndrome. In *Fifth International Conference on Sarcoidosis*. Edited by L. Levinsky and F. Macholda. Univ Karlova, Prague, 1971, p. 469.
5. Fajgelj, I., and Djuric, B.: Simultaneous Biopsy of Mediastinal Lymph Nodes, Lungs and Pleura in Sarcoidosis. In *Proceedings of the VI International Conference on Sarcoidosis*. Edited by K. Iwai and Y. Hosoda. Univ Tokyo, Tokyo, 1974, p. 425.
6. Carrington, C. B., Gaensler, E. A., Mikus, J. P., Schachter, A. W., Burke, G. W., and Goff, A. M.: Structure and Function in Sarcoidosis, Ann NY Acad Sci, 278:265, 1976.
7. Longcope, W. T., and Freiman, D. G.: A Study of Sarcoidosis Based on a Combined Investigation of 160 Cases Including 30 Autopsies from The Johns Hopkins Hospital and Massachusetts General Hospital, Medicine 31:1, 1952.
8. Miller, A., Chuang, M., Teirstein, A. S.: Two Unusual Presentations of Granulomatous Lung Disease. First Pan-American Congress on Diseases of the Chest, Lima, Peru, June 3, 1976.
9. AlBazzaz, F., Werner, P., Williams, J. F., Johnson, D. H., Lourenco, R. V.: Closing Volume in Pulmonary Sarcoidosis (abstract), Clin Res 20:757, 1972.
10. Levinson, R. S., Metzger, L. F., Stanley, N. N., Kelsen, S. G., Altose, M. D., Cherniack, N. S., and Brody, J. S.: Airway Function in Sarcoidosis, Amer J Med 62:51, 1977.
11. Marshall, R., Smellie, H., Baylis, J. H., Hoyle, C., and Bates, D. V.: Pulmonary Function in Sarcoidosis, Thorax 13:48, 1958.
12. Young, R. L., Harkleroad, L. E., Lordon, R. E., and Weg, J. G.: Pulmonary Sarcoidosis: A Prospective Evaluation of Glucocorticoid Therapy, Ann Int Med 73:207, 1970.
13. Israel, H. L.: The Treatment of Sarcoidosis, Postgrad Med J 46:537, 1970.
14. Israel, H. L., Fouts, D. W., and Beggs, R. A.: A Controlled Trial of Prednisone Treatment of Sarcoidosis, Amer Rev Resp Dis 107:609, 1973.
15. Turiaf, J.: The Problem of the Treatment of Sarcoidosis: Report of the Subcommittee on Therapy, Ann NY Acad Sci, 278:743, 1976.
16. Johns, C. J., MacGregor, M. I., Zachary, J. B., and Ball, W. C.: Extended Experience in the Long-Term Corticosteroid Treatment of Pulmonary Sarcoidosis, Ann NY Acad Sci, 278:722, 1976.
17. Revfem, O.: Long-Term Corticosteroid Treatment of Pulmonary Sarcoidosis. In *Proceedings of the Sixth International Conference on Sarcoidosis*. Edited by K. Iwai and Y. Hosoda. University of Tokyo Press, Tokyo, 1975, p. 547.

18. De Remee, R. A.: The Present Status of Treatment of Pulmonary Sarcoidosis: A House Divided, Chest 71:388, 1977.
19. Stone, D. J., Schwartz, A., Feltman, J. A., and Lovelock, F. J.: Pulmonary Function in Sarcoidosis, Amer J Med 15:468, 1953.
20. Emirgil, C., Sobol, B. J., and Williams, M. H., Jr.: Long-Term Study of Pulmonary Sarcoidosis: The Effect of Steroid Therapy as Evaluated by Pulmonary Function Studies, J Chron Dis 22:69, 1969.
21. Sharma, O. P., Colp, C., Williams, M. H., Jr.: Course of Pulmonary Sarcoidosis With and Without Corticosteroid Therapy as Determined by Pulmonary Function Studies, Amer J Med 41:541, 1966.
22. Colp, C., Park, S. S., Williams, M. H., Jr.: Pulmonary Function Follow-Up of 120 Patients with Sarcoidosis, Ann NY Acad Sci 278:301, 1976.
23. Emirgil, C., Sobol, B. J., Herbert, W. H.,and Trout, K.: The Lesser Circulation in Pulmonary Fibrosis Secondary to Sarcoidosis and its Relationship to Respiratory Function, Chest 60:371, 1971.

The Mount Sinai Journal of Medicine
Vol. 44, No. 6, November-December, 1977
Printed in U.S.A.

CIGARETTE SMOKING AND THE LUNGS*

ROSCOE C. YOUNG, JR., M.D.

Introduction

I am privileged to have been accorded the honor of paying tribute to Professor Louis E. Siltzbach, a tireless crusader in the fight against respiratory diseases. This brief salute is presented to recognize his influence and efforts in all respiratory directions. Cigarette lung diseases, unlike sarcoidosis, are of known causation and therefore theoretically preventable.

Background

Tobacco was first cultivated by the North and South American Indians. When Columbus and other explorers arrived, they found tobacco used much the same manner as it is today. It was thought to contain medicinal properties. The "peace pipe" among American Indians had symbolic significance among their rites and rituals. The introduction of tobacco to other parts of the world through Europe began in France in 1556. Thirty years later, Ralph Lane, first Governor of Virginia brought an Indian pipe to Sir Walter Raleigh and taught him how to use it.

In 1963, Dr. Luther L. Terry, then Surgeon General of the USPHS, released his famous 387-page report on Smoking and Health (1). Education and warnings that cigarette smoking may be hazardous to health have been largely ineffective. The Federal Trade Commission expected final figures on cigarette consumption for the year 1973 to show the largest yearly increase since the Surgeon General's Report. In its required year-end report to Congress, the Commission noted the 1973 consumption up 3.8 percent, making total consumption in the United States greater than 582 billion cigarettes. The 1972 total was 562 billion (2): Since 1973, the percent of adult smokers has declined, however the total number of persons who still smoke is on the increase. There were 875,000 more smokers in the United States in 1975 than in 1970.

Pharmacology

Cigarette smoke is a heterogeneous mixture of gases, uncondensed vapors and liquid, and particulate matter, whose median particle size is 0.5 μ. Tobacco tars contain all the particulate phase of smoke as well as condensable components of the gas phase. The amount of tar from one cigarette is between 3 and 4 mg depending on burning conditions, cigarette length, whether the cigarette in question is a filter cigarette or not, porosity of paper, and type of tobacco.

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* Presented to the Board of Directors, District of Columbia Lung Association, January 19, 1977.

From the Department of Medicine and the Harden Pulmonary Laboratory, Howard University Hospital, Washington, D. C. 20060.

The Federal Trade Commission has released data on tar and nicotine content of brands sold in this country for March 1974. Over 500 different compounds occur in cigarette smoke, including nicotine and its related companion alkalosis, noncarcinogenic hydrocarbons, carcinogenic hydrocarbons, terepene and isoprenoid hydrocarbons, alcohols and esters, sterols, aldehydes and ketones, acids, and gases, including carbon monoxide and acroline (1).

It may be well to discuss the pharmacology of two of the compounds, nicotine and CO, and add one that occurs in cigarette smoke only in trace amounts, but appears to exercise some influence as a carcinogen by causing radioactivity. This is polonium^{210} and will be discussed later.

The acute effects of nicotine in small doses (1–2 mg/cigarette) are small and represent the sum of stimulant and depressant effects on several organ systems. Nicotine usually causes an increase in respiratory rate, rise in systolic blood pressure, anorexia, and in larger doses, nausea and vomiting. It is absorbed and exerts its effects in 4 areas of the body.

It acts on peripheral chemoreceptors to cause hyperpnea and hypertension on one hand, and on thoracic chemoreflexes, now known to be Type J pulmonary receptors, to cause hypotension, bradycardia, and apnea on the other. Further, apnea and central nausea and vomiting are caused by its action on the brain stem. Death from *high* doses of nicotine is due to respiratory failure because of paralysis of nerve cells at the myoneural junction, curare-like action (3). A small amount of nicotine injected into the common carotid artery of the dog causes an increase in tidal volume, frequency and minute volume, decrease in alveolar CO_2, and bradycardia by carotid body stimulation.

In heavy cigarette smokers carbon monoxide may be absorbed to form carboxyhemoglobin (COHb) to the extent of 5 to 10 percent of the total hemoglobin in the blood. Although it decreases the partial pressure of oxygen by only a small amount, it impairs oxygen delivery to the tissues by decreasing the amount of oxygen released to the tissues by decreasing P50 of the oxyhemoglobin dissociation curve. Hemoglobin is completely saturated with CO at partial pressures less than 1 mm Hg.

Prior to the beginning of the last decade, it was not recognized that COHb levels below 10 percent caused impairment, but recently, thinking on this subject has been reversed. Psychological tests have noted changes in vision, impairment in fine discrimination, and cardiovascular effects at those concentrations. Implications regarding split-second decisions while driving and in patients with preexisting anemia or cardiopulmonary disease are evident (4).

Altered Physiology

The effects of smoking are measurable on the intact patient. Acutely, cigarette smoking has been found to increase the resistance to air flow in the bronchi. The effect is due to the irritant effect of sub-micronic particles on large airways. It is reflexly mediated via vagal pathways, and can be blocked by atropine and reversed by isoproterenol, or by taking a deep breath, as shown by body plethysmograph studies (5).

No discussion of cigarette smoking would be complete without mentioning marijuana smoking, a practice more widespread among young people than realized. Information on marijuana smoking is rare, and carefully controlled studies are just beginning to emerge (6, 7). Acutely, marijuana and its active ingredient, 9 delta Tetrahydrocannabinol (THC), cause bronchodilatation, (in contrast to bronchoconstriction caused by tobacco), and an increase in heart rate. Unlike opiates it does not depress respiration by central action. Tashkin and coworkers (7) compared the increase in percent specific conductance as a function of time after simulated marijuana smoking, isoproterenol and 2 percent marijuana. The increase in air-ways conductance was greater for marijuana than it was for 1:200 isoproterenol and conductance fell after smoking a tobacco cigarette.

The results of these studies raise questions of the efficacy of marijuana use in asthma. The chronic effects of chromosomal damage in leukocytes and immunosuppression of cellular immunity combined with social implications of its illegality may outweigh any benefit of acute respiratory effects. Chronic marijuana use, however, may cause chronic bronchitis, indistinguishable from that caused by cigarette smoking.

Recently tests designed to measure resistance in small peripheral airways have shown that these airways can be obstructed when gross tests fail to demonstrate involvement of larger airways. Cigarette smokers may have a higher closing volume at any age, or fail to demonstrate one (8).

Woolcock and associates (9) demonstrated small airways obstruction in 5 bronchitic subjects, all heavy cigarette smokers, by showing that the dynamic lung compliance becomes frequency-dependent when expressed as percent of static lung compliance.

Krumholtz and associates (10) showed that static mechanical properties of lungs of smokers may be different from that of nonsmokers. They measured the "stiffness" of the lungs during breathing of 10 young cigarette smokers and an equal number of nonsmokers. The lungs of the smokers were found to be stiffer than the lungs of nonsmokers as indicated by a lower compliance when corrected for lung size (a mean specific compliance of 0.042 for smokers as compared with 0.054 for nonsmokers). They interpreted the behavior as suggesting that the small airways are plugged, and the lung behaves for purposes of pressure volume measurement as though it were smaller. McFadden and coworkers (11) studied lung function in 53 patients who were chronic bronchitis and heavy cigarette smokers. The only abnormalities on routine studies were a decreased maximal mid-expiratory flow rate and increased residual volume. Gross parameters of airways obstruction, FEV_1 and airways conductance were normal. They showed that cessation of smoking combined with bronchodilators completely reversed all abnormalities in 4 subjects. These workers suggested that measurements of maximal mid expiratory flow rates as part of routine tests may detect significant obstruction of small peripheral airways, an abnormality frequently seen in heavy cigarette smokers.

The ability of the lung to transfer gases from alveoli into pulmonary capillary blood has also been found to be impaired. Martt (12) showed changes in diffusing capacity due to smoking, the nature of which was thought to be "chronic irritation of the lung membranes." Mean DL for 25 smokers was 25, while that for 30 nonsmoking control subjects was 33 ml/min/mmHg.

The interest centered about performance of respiratory measurements on smokers and nonsmokers in an effort to detect chronic bronchitis and emphysema early in its natural history when reversal of abnormalities may be possible.

Airways Obstruction

Cigarette smoking is the most important cause of chronic bronchitis in the United States and a relationship exists between smoking and pulmonary emphysema. Clinical and anatomical relationship of chronic bronchitis and emphysema to number of cigarettes smoked has been made repeatedly (13, 14). The percent prevalence of COPD rises from 20 percent in men who never smoked, to 88 percent in those smoking over two packs of cigarettes a day or about 4.5 times that of the nonsmoker. Pipe and cigar smokers have a greater risk of developing RD than nonsmokers, but the risk was not as great as that for cigarette smokers (15). The degree to which smokers inhale definitely shows an increase in prevalence of respiratory disease, the prevalence of RD being greater among heavy smokers of both sexes who inhale. Use of filter cigarettes provides controversial data.

The mechanism of causation of chronic bronchitis and emphysema is by interference with or neutralization of the defenses of the lung. Mucociliary activity of the airways (the mucociliary escalator) is depressed by increased secretion of mucous glands and decrease in ciliary activity. Recent experiments in mice indicate that the acrolein component of cigarette smoke not only depresses pulmonary bactericidal activity, but also synergistically aggravates underlying pulmonary infection and causes additional impairment of pulmonary defenses (16). In addition, cigarette smoke inhibits phagocytic activity of alveolar macrophages. Green and Carolin (17) have demonstrated that small amounts of cigarette smoke quatitatively inhibits the capacity of rabbit alveolar macrophages to inactivate staphlococcus albus bacteria in vitro. The experiment suggests that the role of cigarette smoke in the pathogenesis of pulmonary disease may be "the integrated defense function at the respiratory membrane level of the lung."

Surfactant and yield of its lethicin precursor have been found decreased in smokers after endobronchial lavage with a return to nonsmoker levels after cessation (18). It is possible that smoke exerts a temporary nonspecific toxic effect on type II alveolar cells. The relationship, however, between decreased surfactant in smokers and the clinical conditions under consideration remains uncertain.

The manner in which the environmental influence of cigarette smoke combines with genetic factors to produce emphysema in a small group (1 to 2 percent of patients) has been suggested. Cigarette smoke may enhance the inflammatory exudate of leukocytes and macrophages, as discussed earlier by inhibiting bacterial clearance from alveoli by macrophages. These leucocytes, sequestered in the bases of the lung where blood flow is greatest, may release their proteases on unprotected lung with genetically determined partial $alpha_1$ antitrypsin deficiency (heterozygotes), thus causing emphysema earlier, than it would have, if no genetic deficiency existed.

A special type of asthma noted in post-World War II U.S. Armed Forces personnel and their dependents stationed in the heavily industrialized Kanto plant area of Japan is characterized by severe cough and paroxysmal dyspnea, poorly reversible with bronchodilators. Relief occurs when leaving the environment and exacerbations occur on return for a second tour of duty (19). "Tokyo-Yokohama asthma" is perpetuated by heavy cigarette smoking and may lead to emphysema. There is little evidence to support an immunologic basis for these attacks, which most likely represent effects of a combination of cigarette smoke and air pollutants on the lungs.

Among occupational groups, cigarette smoking is an important variable that must be considered in all studies of chronic bronchopulmonary disease. In most studies but not all, the relative importance of cigarette smoking is greater than occupational exposures in production of respiratory symptoms and functional abnormalities.

Pulmonary Neoplasia

$Polonium^{210}$ (Po^{210}) is found in trace amounts in cigarette smoke. It is an alpha particle emitting a radioactive element, a naturally occurring daughter isotope of $radium^{226}$ with a half-life of 138 days. Studies by Little and coworkers (20) indicate that the bronchial epithelium of cigarette smokers had higher concentrations of radioactive polonium than did that of nonsmokers, and that concentrations were especially high at segmental bifurcations. The implication being that radiation from a trace element in cigarette smoke such as polonium may be a factor in development of lung cancer.

The risk of development of lung cancer is increased with the duration of smoking and the number of cigarettes smoked daily and is diminished by discontinuing smoking. Recent work by Kellerman and associates (21) has linked genetic determinants to the development of lung cancer, in the form of aryl-hydrocarbon hydroxylase, and inducible membrane-bound enzyme, which metabolizes carcinogenic hydrocarbons to reactive intermediates called "epoxides" with chemical reactivity against DNA and RNA. Susceptibility to lung cancer was found to be associated with higher levels of enzyme activity.

Hammond, Auerbach and associates (22, 23) have shown clear evidence of a dose-response relationship in dogs which is diminished by discontinuing smoking. Extrapolation of these animal studies to man should not be difficult.

The histologic types of lung cancer caused by cigarette smoking are largely of the squamous cell and undifferentiated types. The interaction of smoking with environmental determinants such as asbestos potentiates development of bronchogenic carcinoma.

The only way to combat cigarette smoking with a high success rate may be to change behavioral patterns of the public. Psychological behavioral studies show a relationship between anxiety, depression and emotional insecurity and the need to smoke. The motivations referred to are often stronger than the threat of future death and disease, and have overshadowed efforts to prevent smoking by cessation clinics, mass media, National Interagency Council on Smoking and Health, American Cancer Society, American Lung Association, American Heart Association. These societies through coordinated assistance of psychiatrists, psychologists, social workers and community health experts, may be able to alter behavioral patterns of entire communities to cause a significant reduction in smoking and resultant respiratory disease.

References

1. Terry, L. L.: Smoking and Health. U.S. Public Health Service DHEW, 1963.
2. Newsletter, Brooklyn Tuberculosis and Respiratory Disease Association, February 1974.
3. Comroe, J. H., Jr. and Nadel J.: In *Tobacco and Health.* Edited by James and Rosenthal et al. Charles C. Thomas, Springfield, Illinois, 1962, P. 233.
4. Silver, H. M.: Carbon Monoxide in Health and Politics, Med Ann D C 40:169, 1971.
5. Nadel, J. A. and Tierney, D. F.: Effect of a Previous Deep Inspiration on Airway Resistance in Man, J Appl Physiol 16:717, 1961.
6. Vachon, L., Fitzgerald, M. X., Solliday, N. H., Gould, I. A., and Gaensler, E. A.: Single Dose Effect of Marijuana Smoke, N Engl J Med 288:985, 1973.
7. Tashkin, D. P., Shapiro, B. J., and Frank, I. M.: Pulmonary Effects of Smoked Marijuana and Oral ^{9}-Tetrahydrocannabinol, N Engl J Med 289:336, 1973.
8. McCarthy, D. S., Spencer, R., Greene, R., and Milic-Emili, J.: Measurement of "Closing Volume" as a Simple and Sensitive Test for Early Detection of Small Airways Disease. Am J Med 52:747, 1972.
9. Woolcock, A. J., Vincent, N. J., and Macklem, P. T.: Frequency Dependence of Compliance as a Test for Obstruction of Small Airways, J Clin Invest 48:1097, 1969.
10. Krumholtz, R. A. Chevalier, R. B., and Ross, J. C.: A Comparison of Pulmonary Compliance in Young Smokers and Non-Smokers, Am Rev Respir 92:102, 1965.
11. McFadden, E. R. and Linden, D. A.: A Reduction in Maximal Mid-Expiratory Flow Rate. A Spirographic Manifestation of Small Airway Disease, Am J Med 52:725, 1974.
12. Martt, J. M.: Pulmonary Diffusing Capacity in Cigarette Smokers, Ann. Intern Med 56:39, 1962.
13. Mitchell, R. M., Vincent, T. N., and Filley, G. F.: Cigarette Smoking, Chronic Bronchitis and Emphysema, JAMA 188:132, 1964.
14. Auerbach, O., Hammond, E. C., Garfinkel, L., and Benante, C.: Relation of Smoking and Age to Emphysema, N Engl J Med 286:853, 1972.
15. Anderson, D. O. and Ferris, B. G., Jr.: Role of Tobacco Smoking in the Causation of Chronic Respiratory Disease, N Engl J Med 267:787, 1962.
16. Jakab, G. J.: Adverse Effect of A Cigarette Smoke Component Acrolein on Pulmonary Antibacterial Defenses and on Viral-Bacterial Interactions in the Lung, Am Rev Respir Dis 115:33, 1977.
17. Green, G. M. and Carolin, C.: The Depressant Effect of Cigarette Smoke on the in Vitro Antibacterial Activity of Alveolar Macrophages, N Engl J Med 276:422, 1967.
18. Finley, T. N. and Ladman, A. J.: Low Yield of Pulmonary Surfactant in Cigarette Smokers, N Engl J Med 286:223, 1972.
19. Phelps, H. W. and Koike, S.: "Tokyo-Yokohama Asthma" The Rapid Development of

Respiratory Distress, Presumably Due to Air Pollution, Am Rev Respir Dis 86:55, 1962.

20. Little, J. B., Radford, E. P., McCombs, H. L., and Hunt, V. R.: Polonium^{210} in Pulmonary Tissues of Cigarette Smokers, N Engl J Med 273:1343, 1965.
21. Kellerman, G., Shaw, C. R., and Luyten-Kellerman, M.: Aryl Hydrocarbon Hydroxylase Inducibility and Bronchogenic Carcinoma, N Engl J Med 289:934, 1973.
22. Hammond, E. C., Auerbach, O., Kirman, D., and Garfinkel, L.: Effect of Cigarette Smoking on Dogs I. Design of Experiment, Mortality and Findings in Lung Parenchyma, Arch Environ Health 21:748, 1970.
23. Auerbach, O., Hammond, E. C., Kirman, D. and Garfinkel, L.: Effects of Cigarette Smoking in Dogs II, Pulmonary Neoplasms, Arch Environ Health 21:754, 1970.

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